1085 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 0.90 (3 H, t, CH_3), 1.1-2.45 (20 H, m), 4.05 (3 H, m, CHOH), 5.10 (4 H, s, OH), 5.2-5.7 (4 H, m, olefinic H); mass spectrum, m/z 336 (M - 18), 318, 264; $[\alpha]^{25}D$ +23.8° (THF; c 0.80) [lit.[7f] +23.5° in THF]. This material proved to be in all respects identical with an authentic sample[24] of $PGF_{2\alpha}$.

Characterization of the second compound (the faster running band in the preparative tlc plate) presumably 15-epi-$PGF_{2\alpha}$ was not undertaken.

(b) By Wittig Coupling of 41 with 43. To a solution of **31** (0.3 g; prepared as described above) in methylene chloride (5 mL) was added dihydropyran (1.0 mL) together with anhydrous *p*-toluenesulfonic acid (~10 mg). The mixture was stirred at 20 °C until TLC analysis indicated that no starting material was present (1 h). The solution was then washed with saturated sodium bicarbonate solution and evaporated to dryness to give essentially pure **43** as a viscous oil (0.4 g). TLC analysis (SiO_2; Et_2O; R_f 0.3) showed the presence of only one spot. This material was used as follows.

A solution of the (*S*)-(+)-phosphonium salt **41** (0.8 g) in dry tetrahydrofuran (10 mL) was cooled to -78 °C under N_2 and treated with 2 equiv of butyllithium in ether (2.4 mL solution). The temperature was allowed to rise to -20 °C and then after 30 min was lowered again to -78 °C. To this solution there was added during 7 min a solution of **43** (0.4 g) in tetrahydrofuran (5 mL). The temperature was allowed to rise to 0 °C and, after a further 30 min at room temperature, the solvent was removed under reduced pressure at <20 °C. The residue was treated with 50% aqueous acetic acid (5 mL) and heated to 50 °C for 1 h. Water (15 mL) was then added and the mixture extracted with ethyl acetate (3 × 10 mL). The extract was washed with sodium bicarbonate solution (5 mL) and then dried ($MgSO_4$). For removal of traces of phosphorus compounds, the solution was perolated through a column of silica gel (10 g). The column was washed with additional ethyl acetate (10 mL), and the combined solutions were evaporated to dryness to give a glassy solid (0.37 g). Hydrolysis of this material using potassium hydroxide was accomplished essentially as described in method a except that the neutralization afterward was done by titration with 1 N hydrochloric acid. The material (0.33 g) isolated by ethyl acetate extraction was then subjected to preparative TLC separation (SiO_2; ethyl acetate/methanol/formic acid, 95:4.5:0.5) using authentic (+)-$PGF_{2\alpha}$ as a marker. Much less polar material was present. The band corresponding to $PGF_{2\alpha}$ was extracted to give the crude oily material (56 mg). Further purification was effected via a second preparative TLC. The purified product (42 mg, 12% yield) had $[\alpha]^{25}_D$ +24.3° (THF; c 1.03) and was in all respects identical with the sample prepared as described in method a.

Acknowledgment. We wish to thank F. Battaglia, V. Ferri, and M. Cellentani for their technical assistance. The following people are gratefully acknowledged for providing physical data: Miss A. De Paoli (NMR), Dr. M. Landi (GC-MS and GC), Dr. L. Zerilli and Mr. G. Tuan (MS), Dr. P. Ferrari (IR), Mr. P. Gironi (optical rotation), and Mr. E. Petressi (microanalysis). We also wish to thank Drs. S. W. Tobey and G. Nathansohn for their encouragement throughout this work.

Registry No. 1a, 58096-39-2; **1b**, 59025-04-6; **2a**, 58096-40-5; **2b**, 59025-05-7; **7**, 59042-97-6; **9**, 58683-43-5; **10**, 59042-99-8; **11**, 58683-45-7; **12**, 59043-00-4; **13**, 58717-38-7; **14**, 26054-65-9; **18**, 80800-64-2; **19**, isomer 1, 80844-93-5; **19**, isomer 2, 80844-94-6; **20**, 67718-97-2; **24a**, 80844-95-7; **24b**, 53275-75-5; **25**, 67842-98-2; **26**, 51638-25-6; **28**, 41723-91-5; **29**, 63162-87-8; **29** methyl ester, 66101-25-5; **30**, 61408-41-1; **31**, 61408-40-0; **32**, 80800-65-3; **33**, 551-11-1; **34**, 37658-84-7; **35**, 15186-48-8; **36**, 78918-73-7; **37**, 61228-99-7; **38**, 61229-00-3; **39**, 80800-66-4; **40**, 80800-67-5; **41**, 80800-68-6; **43**, 61218-06-2; isopropyl bromide, 75-26-3; potassium methyl malonate, 38330-80-2; succinyl chloride, 543-20-4; (*S*)-malic acid, 97-67-6; ethyl bromide, 74-96-4; methyl hydrogen malonate, 16695-14-0; dimethyl (2-oxoheptyl)-phosphonate, 36969-89-8.

Stereoselective Total Synthesis of (±)-Gymnomitrol via Reduction-Alkylation of α-Cyano Ketones

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Abstract: A 16-step total synthesis of the tricyclic sesquiterpene alcohol, gymnomitrol (**1**), from *cis*-tetrahydro-3a,6a-dimethyl-2,5(1*H*,3*H*)-pentalenedione (**8**) is described. Catalytic hydrogenation of the monoenol phosphate of **8** afforded the monoketone, *cis*-hexahydro-3a,6a-dimethyl-2(1*H*)-pentalenone (**7**). Reduction-allylation of the α-(*n*-butylthio)methylene derivative of **7** gave allyl trimethyl ketone **14a** having the allyl substituent in the exo orientation. The stereoisomer (**19**) of **14a** was obtained by reduction-methylation of α-allyl α-cyano ketone **18**. Ring closure was accomplished by conversion of the allyl trimethyl ketones, **14a** and **19**, to keto aldehydes **23** and **6**, aldol cyclizations, and oxidation to give the isomeric bridged diketones **25** and **29**, respectively. A more efficient synthesis of keto aldehyde **6** was based upon a Michael-like condensation of α-cyano ketone **16** with acrolein diethyl acetal which gave rise to α-ethoxyallyl α-cyano ketone **34**. The enol ether in the side chain was converted to an ethylene acetal, the resulting α-cyano ketone (**36**) was subjected to reduction-methylation, and the acetal was hydrolyzed, affording keto aldehyde **6**. Enol lactone **39**, prepared from the corresponding keto acid (**38**), underwent efficient aldol cyclization upon reduction with diisobutylaluminum hydride, and the ketol so obtained was oxidized to bridged diketone **29**. The synthesis of (±)-gymnomitrol was completed by regioselective addition of methyllithium to diketone **29**, dehydration, and hydride reduction.

The isolation of the novel tricylcic sesquiterpenes, (+)-gymnomitrol (**1**), (-)-β-gymnomitrene (**2**), and a number of more highly oxygenated derivatives, from the liverwort *Gymnomitrion obtusum* (Lindb) Pears, and the determination of their structures by chemical degradation and spectroscopic evidence was reported by Connolly, Harding, and Thornton in 1970.[1] Shortly thereafter (-)-β-gymnomitrene (also known as β-barbatene and β-pompene) and its endocyclic isomer were isolated from other species of liverwort in three different laboratories.[2-4] The structure of (+)-α-gymnomitrene (α-pompene) was established firmly by an X-ray crystallographic determination of a diol mono-*p*-bromobenzoate derivative.[3b,d] The only other sesquiterpene known to possess the decahydro-4,8-methanoazulene ring system of gymnomitrol is α-caryophyllene alcohol[5] which has a different methyl

(1) Connolly, J. D.; Harding, A. E.; Thornton, I. M. S. *Chem. Commun.* **1970**, 1320-1321; *J. Chem. Soc., Perkin Trans. 1* **1974**, 2487-2493.

(2) (a) Andersen, N. H.; Huneck, S. *Phytochemistry* **1973**, *12*, 1818-1819. (b) Andersen, N. H.; Costin, C. R.; Kramer, M., Jr.; Ohta, Y.; Huneck, S. *Ibid.* **1973**, *12*, 2709-2716.

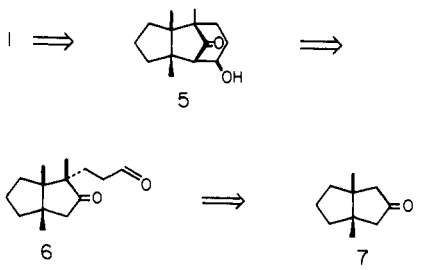
(3) (a) Matsuo, A.; Maeda, T.; Nakayama, M.; Hayashi, S. *Tetrahedron Lett.* **1973**, 4131-4134. (b) Matsuo, A.; Nozaki, H.; Nakayama, M.; Kushi, Y.; Hayashi, S.; Kamijo, N. *Ibid.* **1975**, 241-244. (c) Matsuo, A.; Uto, S.; Nakayama, M.; Hayashi, S. *Z. Naturforsch., C:Biosci* **1976**, *31C*, 401-402. (d) Nozaki, H.; Matsuo, A.; Nakayama, M.; Kushi, Y.; Kamijo, N.; Hayashi, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 568-574.

(4) Paknikar, S. K.; Kirtany, J. K.; Naik, C. G. *Ind. J. Chem.* **1975**, *13*, 1234.

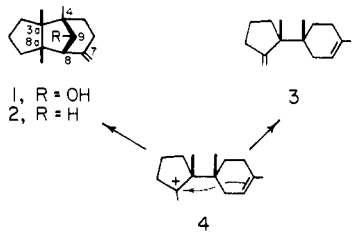
(5) Adams, D. R.; Bhatragar, S. P.; Cookson, R. C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1502-1506.

0002-7863/82/1504-2198$01.25/0

Scheme I



group substitution pattern and biogenetic origin. The most likely biogenesis of gymnomitrene involves a π cyclization of bicyclic cation **4** (or its equivalent),[1,6] a supposition consistent with its cooccurrence with bazzanene (**3**) in *Bazzania pompeana*.[6] These natural products therefore belong to the cuparene family of sesquiterpenes.

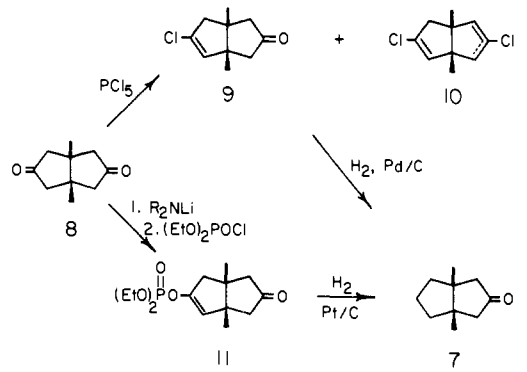


The interesting carbon skeleton and biogenesis of gymnomitrol stimulated us to undertake a total synthesis of this sesquiterpene alcohol.[7,8] The total synthesis would also lend support to the structural assignment, which, in the absence of a direct correlation between **1** and **2**,[9] was based entirely upon deductions from chemical and spectral evidence.[1]

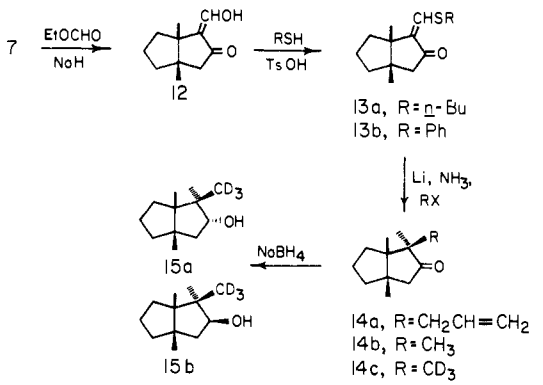
The general plan of the synthesis is depicted in the retrosynthetic analysis in Scheme I. The 1,3 relationship of the double bond and hydroxyl group suggested that an aldol cyclization of keto aldehyde **6** would serve to form the decahydro-4,8-methanozulene nucleus. Keto aldehyde **6** would in turn be accessible via regio- and stereoselective α,α-dialkylation of the known bicyclic ketone **7**.[10] Since the reduction of gymnomitrone with sodium borohydride reestablishes the natural configuration at C-9,[1,11] the only stereochemical problem to be faced in this approach is associated with the geminal dialkylation (**7** → **6**).

Diketone **8** is readily available in substantial quantity by 2:1 condensation of dimethyl acetonedicarboxylate with biacetyl and subsequent hydrolysis and decarboxylation.[12] Since the procedures reported for the conversion of **8** to **7** did not appear suitable for

Scheme II



Scheme III



preparative scale,[10] we investigated three methods for the selective deoxygenation of diketone **8**. Ketalization of **8** with 1.6 equiv of 2,2-dimethylpropane-1,3-diol afforded mono- and bisketals in a 1:3 ratio which were isolated in 21% and 62% yields, respectively, by column chromatography. Wolff–Kishner reduction of the monoketal followed by hydrolysis provided ketone **7** in 70% yield. Although the overall yield could be increased by hydrolysis of the bisketal back to **8** and recycling, the tedious chromatographic separation rendered this process inconvenient. The reaction of diketone **8** with 0.35 equiv of phosphorous pentachloride[13] in chloroform at room temperature produced a mixture of monochloro ketone **9** and dichloro diene **10** in a 3:1 ratio, along with unreacted diketone (Scheme II). This method had the advantage that diketone **8** could be simply recovered by crystallization and then recycled. Catalytic hydrogenation[14] of the monochloro ketone to **7** was accomplished in 65% yield with palladium on carbon in methanol.

The observation that the monoenolate anion of **8** could be selectively formed with 1 equiv of lithium hexamethyldisilamide in tetrahydrofuran (THF) at −78 °C lead to the development of a more efficient preparation. Phosphorylation of the monoenolate with diethyl chlorophosphate followed by catalytic hydrogenation[15] of the resulting unpurified enol phosphate (**11**) with 5% platinum on carbon in ethyl acetate under 5 atm of pressure gave monoketone **7** in 77% overall yield.

The first stage of the synthesis was the geminal dialkylation of **7** with a methyl group and a 3-carbon appendage suitable for elaboration to a propionaldehyde substituent. Since the α-carbon of **7** is rather sterically hindered, we initially chose to utilize an allyl substituent in order to facilitate formation of the third contiguous quaternary carbon by enolate allylation. The stereoselectivity to be expected in the alkylations was uncertain owing to the presence of the two ring juncture methyl groups.

(6) Matsuo, A.; Hayashi, S. *J. Chem. Soc., Chem. Commun.* **1977**, 566–568.

(7) Preliminary communication: Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1979**, *101*, 6765–6767. Some aspects of this research have also appeared in a review on polyquinanes. See: Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41–165.

(8) For other recent syntheses of gymnomitrol and/or gymnomitrene see: (a) Büchi, G.; Chu, P.-S. *J. Am. Chem. Soc.* **1979**, *101*, 6767–6768. (b) Welch, S. C.; Chayabunjonglerd, S. *Ibid.* **1979**, *101*, 6768–6769. (c) Welch, S. C.; Chayabunjonglerd, S.; Prakasa Rao, A. S. C. *J. Org. Chem.* **1980**, *45*, 4086–4093. (d) Han, Y.-K.; Paquette, L. A. *Ibid.* **1979**, *44* 3731–3733. Paquette, L. A.; Han, Y.-K. *J. Am. Chem. Soc.* **1981**, *103*, 1831–1835. (e) Kodama, M.; Kurihara, T.; Sasaki, J.; Ito, S. *Can. J. Chem.* **1979**, *57*, 3343–3345. (f) Büchi, G.; Chu, P.-S. *Tetrahedron* **1981**, *37*, 4509–4513.

(9) Recent syntheses[8c,e] of gymnomitrene and gymnomitrol from common intermediates constitute correlations between the racemic forms of the natural products.

(10) Borden, W. T.; Ravindranathen, T. *J. Org. Chem.* **1971**, *36*, 4125–4127.

(11) Gymnomitrol and other tricyclic compounds described in this paper have been named and numbered as derivatives of decahydro-4,8-methanoazulene. Unfortunately the order of the positional numbers in the systematic nomenclature used by Chemical Abstracts varies according to the functionality and substituents present.

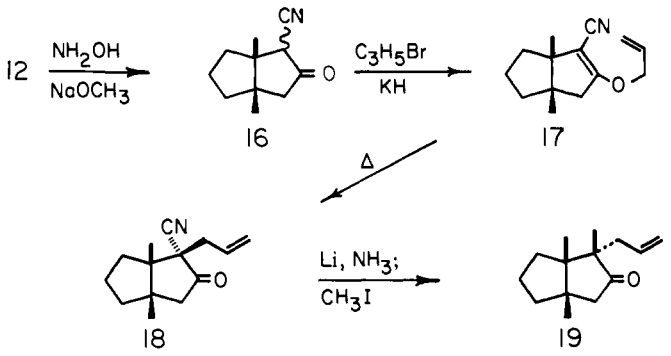
(12) (a) Weiss, U.; Edwards, T. M. *Tetrahedron Lett.* **1968**, 4885–4887. (b) Baldwin, J. E.; Kaplan, M. S. *J. Am. Chem. Soc.* **1971**, *93*, 3969–3977.

(13) Pospíšek, J.; Veselý, Z.; Trojánek, J. *Collect. Czech. Chem. Commun.* **1968**, *33*, 76–82.

(14) Manatt, S. L.; Vogel, M.; Knutson, D.; Roberts, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 2645–26.

(15) Jung, A.; Engel, R. *J. Org. Chem.* **1975**, *40*, 3652–3654.

Scheme IV

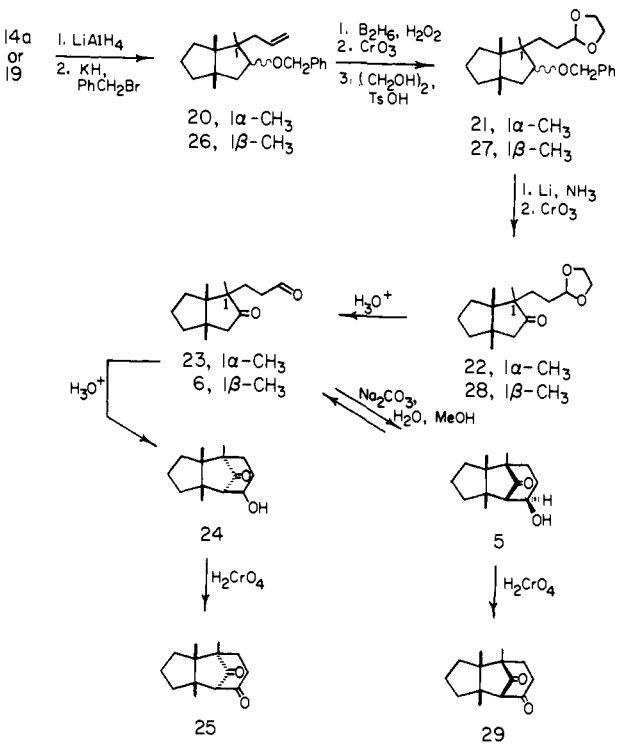


α-Hydroxymethylene ketone **12** was prepared (83%) by condensation of **7** with ethyl formate and sodium hydride in THF and was converted to the α-thiomethylene ketones **13a** (84%) and **13b** (94%) by reaction with the corresponding thiols (Scheme III).[16] Reduction of either **13a** or **13b** with lithium in liquid ammonia and 1,2-dimethoxyethane at −33 °C generated the methyl-substituted enolate anion[17] which underwent regio- and stereoselective allylation with allyl bromide to give a single dialkylated ketone (**14a**) in 26–49% yield. Similar reduction–alkylation with methyl iodide and trideuteriomethyl iodide afforded tetramethyl ketones **14b** and **14c**. The formation of stereochemically homogeneous ketones **14a** and **14c** demonstrated clearly that reactions of enolate anions of this hexahydropentalenone are in fact highly stereoselective and it seemed probable that carbon–carbon bond formation occurred on the exo face despite the presence of two angular methyl groups.

Evidence consistent with the exo position of the trideuteriomethyl group in **14c** was obtained from europium(III) shift gradients[18] for the methyl peaks in NMR spectra of the epimeric alcohols **15a** and **15b** formed by sodium borohydride reduction of **14c**.[19] Since the less polar alcohol **15a** exhibited the largest methyl shift gradient, a cis relationship between the vicinal methyl and hydroxyl groups was readily assigned to this isomer. Although the shift gradients for the four ring juncture methyl groups in the two isomers do not differ greatly, the smallest of the four is shown by the less polar isomer which was taken to indicate a trans stereochemistry between the angular methyls and the hydroxyl group. It follows that the trideuteriomethyl group in **15a** and **15b** is cis to the angular methyls.

The synthesis of the isomeric ketone **19** having the stereochemistry corresponding to **6** required introduction of the allyl group first and the methyl group second. This was accomplished by alkylation–reduction–alkylation of α-cyano ketone **16** (Scheme IV), a procedure which constitutes a new method for regioselective geminal dialkylation of ketones. α-Cyano ketone **16** was prepared in 89% yield by reaction of **12** with hydroxylamine and sodium methoxide in methanol at reflux. Although the potassium enolate anion of **16** reacted with allyl bromide at oxygen affording enol ether **17** (77%), the required *C*-allyl isomer **20** was readily obtained by Claisen rearrangement in benzene at 122 °C (70%). The exo configuration of the allyl group in **18** is tentatively assigned on the assumption that the steric factors which dictate the stereochemistry of the enolate alkylations will affect the [3,3] rearrangement in a similar manner. Lithium–ammonia reductlon of cyano ketone **18**[20] followed by methylation of the resulting lithium enolate anion with methyl iodide in THF at room temperature

Scheme V



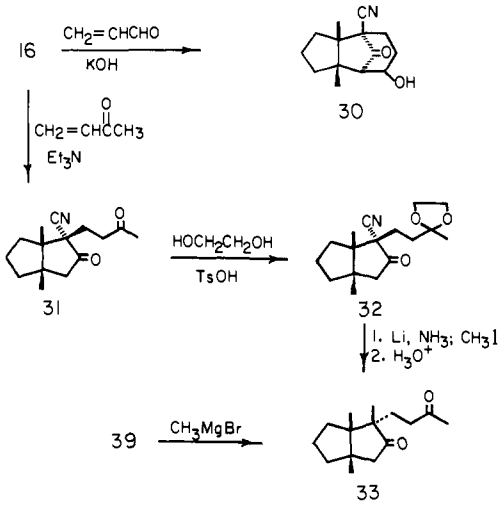
furnished the isomeric ketone **19** in ca. 40–50% yield.

The two isomeric allyl trimethyl ketones **14** and **19** were converted to the corresponding keto acetals **22** and **28** by the same seven-step reaction sequence in 23–25% overall yield, respectively (see Scheme V). Hydrolysis of keto acetal **22** with hydrochloric acid in aqueous acetone at reflux effected removal of the protecting group and concomitant aldol cyclization. The resulting bridged ketol **24** was oxidized with chromic acid to the crystalline diketone **25** in 55% overall yield.[21] Although the IR and NMR spectral characteristics of **25** are quite similar to those of the nordiketone obtained previously from gymnomitrol,[1,22] small differences in the chemical shifts for the three methyl groups demonstrated that the stereochemistry of the three-carbon bridge in **25** is in fact opposite to that of the natural product.

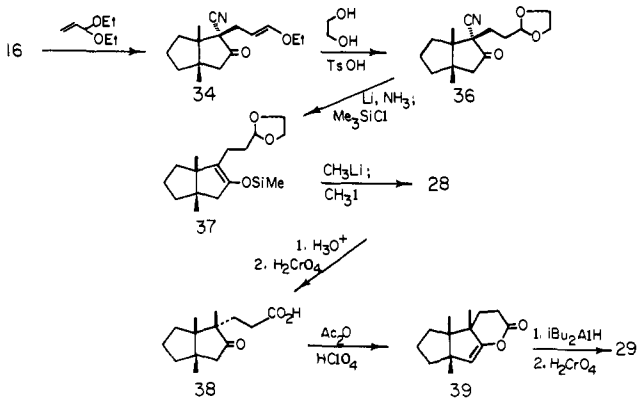
Ring closure of the isomeric keto aldehyde with the correct stereochemistry proved to be more difficult. Hydrolysis of the endo keto acetal **28** under the same conditions which lead to complete cyclization of **23** afforded only keto aldehyde **6**. Attempts to effect the aldol cyclization of this compound under a variety of acidic and basic conditions were unsuccessful. However, exposure of the keto aldehyde to sodium carbonate in 2:1 methanol–water for 3–4 days gave rise to a 3:1 mixture of **6** and the bridged ketol **5** which appeared to be at, or close to, equilibrium.[23] The isomers were separated by column chromatography, the recovered keto aldehyde was recycled, and the bridged ketol was oxidized with chromic acid to the endo-bridged diketone **29** (27% based on unrecovered keto aldehyde). Comparison of the IR and proton NMR spectra of **29** with the corresponding spectra[22] of the optically active diketone of this structure obtained by degradation of gymnomitrol established securely the identity of the two compounds.

(16) Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1615–1619.
(17) Coates, R. M.; Sowerby, R. L. *J. Am. Chem. Soc.* **1971**, *93*, 1027–1029; *Ibid.* **1972**, *94*, 5386–5396.
(18) Shapiro, B. L.; Johnston, M. D.; Jr. *J. Am. Chem. Soc.* **1972**, *94*, 8185–8191.
(19) A similar shift reagent study was also conducted with the epimeric alcohols obtained by hydride reduction of **14a**. However, the data are unfortunately unreliable owing to the small quantities used.
(20) The reductive decyanation of nitriles with metal-ammonia solutions has been reported previously: Arapakos, P. G.; Scott, M. K.; Huber, F. E., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 2059–2062. Marshall, J. A.; Hagan, C. P.; Flynn, G. A. *J. Org. Chem.* **1975**, *40*, 1162–1166.
(21) An independent synthesis of this compound has been reported: Miyashita, M.; Yanami, T.; Kato, M.; Yoshikoshi, A. "Abstracts of the 20th Symposium on the Chemistry of Natural Products"; Chemical Society of Japan: Sendai, Japan, 1976, pp 123–130.
(22) We are grateful to Professor Connolly for providing spectra of the nordiketone **29** and (+)-gymnomitrol as well as comparison samples of **29** and gymnomitryl acetate.
(23) When exposed to the conditions of the aldol cyclization, ketol **5** reverted in part to keto aldehyde **6**. Some retro Micheal reaction also apparently occurred under the aldol cyclization conditions to form a trimethylhexahydro-2(1*H*)-pentalenone.

Scheme VI



Scheme VII



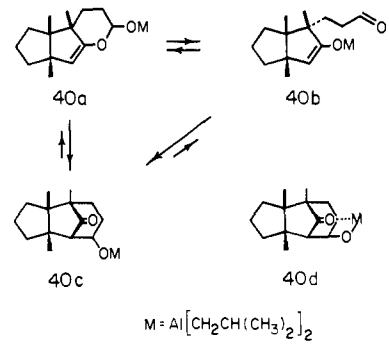
The reluctance of keto aldehyde **6** to undergo aldol cyclization to form a six-membered ring is unusual. Examination of models in fact reveals severe steric interactions between the three bridging carbons of the six-membered ring and the trimethylene carbons. Recent empirical force field calculations by Osawa et al.[24] indicate that the parent hydrocarbon, *cis,endo*-decahydro-4,8-methanoazulene, has a strain energy 5.8–6.7 kcal/mol greater than that of its cis,exo isomer.

As a consequence of the number of steps involved in the synthesis of keto aldehyde **6**, the low yield in the cyclization, and difficulties encountered in subsequent stages, improvements in the efficiency of the synthetic route became mandatory. Introduction of a three-carbon appendage having the terminal position in the correct oxidation state would represent a substantial simplification. The Michael reactions of cyano ketone **16** with acrolein and methyl vinyl ketone were studied with this objective in mind (Scheme VI). Unfortunately the adduct with acrolein underwent further cyclization to exo-bridged ketol **30** (54%) under the conditions used.

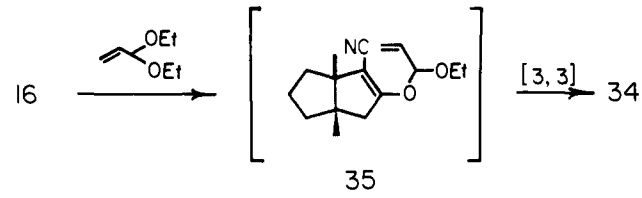
The triethylamine-catalyzed Michael reaction of **16** with methyl vinyl ketone in benzene at room temperature afforded cyano diketone **31** (61%), the side chain carbonyl of which was protected by ketalization with ethylene glycol. Lithium–ammonia reduction of the resulting cyano ketone (**32**) followed by methylation with methyl iodide and hydrolysis gave trimethyl diketone **33** (31% from **31**). The same compound was also prepared by addition of methyllithium to the aldehyde of **6** and subsequent oxidation with chromic acid. However, all attempts to effect an aldol cyclization of diketone **33** were unsuccessful. In this case, the equilibrium probably lies far to the side of the diketone.

(24) Osawa, E.; Aigama, K.; Naotake, T.; Inamoto, Y.; Fujikura, Y.; Majerski, Z.; Schleyer, P. v. R.; Engler, E. M.; Farcasiu, M. *J. Am. Chem. Soc.* **1977**, *99*, 5361–5373.

Scheme VIII



Since a Claisen rearrangement had been employed in the synthesis of cyano ketone **18**, it occurred to us that a similar rearrangement of an α-alkoxyallyl enol ether would give rise to a properly functionallzed side chain. When cyano ketone **18** was heated with 3 equiv of acrolein diethyl acetal in refluxing benzene for 22 h, ethoxyallyl ketone **34** was obtained in 76% yield (Scheme VII). A reasonable mechanism for this interesting variant of the Michael reaction consists of acetal exchange with the enol form of **16** to give ethoxyallyl enol ether **35** followed by [3,3] sigmatropic rearrangement to **34**.[25] However, a direct Michael-type coupling of the α-carbon of **16** to the γ-carbon of an oxonium ion derived



from acrolein diethyl acetal remains a plausible alternative.

The ethoxyallyl ketone **34** was converted to the nicely crystalline acetal **36** by treatment with ethylene glycol in ether containing concentrated hydrochloric acid. Lithium–ammonia reduction of cyano ketone **36** was employed once again to form the enolate anion which in this case was best trapped first by silylation (86%). Regeneration of the lithium enolate from enol silane **37** with methyllithium in THF at 0–25 °C and subsequent methylation gave keto acetal **28** (65%). This four-step route from cyano ketone **16** to **28** represents a substantial improvement in both yield and time compared to the previous 11-step pathway (Schemes IV and V).

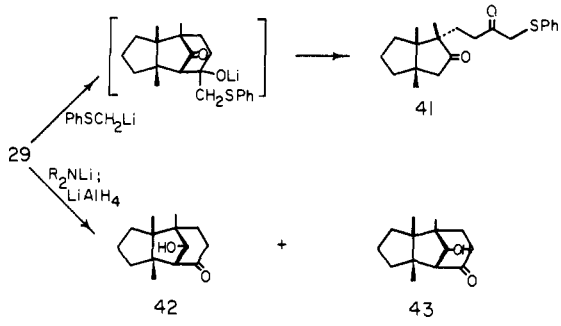
In order to improve the efficiency of the final ring closure, we explored an alternative approach via reduction of enol lactone **39** (Scheme VII).[26] Keto acid **38**, prepared in 92% yield by oxidation of keto aldehyde **6** with chromic acid, was cyclized to the crystalline enol lactone **39** (64%) with acetic anhydride and perchloric acid at 0 °C.[27] Reduction of **39** with diisobutylaluminum hydride[26d] in THF from −78 to 0 °C afforded, after hydrolysis with aqueous hydrochloric acid, the same bridged ketol **5** obtained previously from the aldol cyclization of keto aldehyde **6**. Since the absorption for the carbinyl proton at C-5 in the NMR spectrum of **5** appeared as a broad triplet (δ 4.33) with $J \approx 4.5$ Hz and $W_{1/2} \approx 11$ Hz, the configuration of the hydroxyl is evidently axial[28] in accord with the stereochemistry of other enol

(25) Precedent for this type of transformation may be found in the following references: (a) Dolby, L. J.; Elliger, C. A.; Esfandri, S.; Marshall, K. S. *J. Org. Chem.* **1968**, *33*, 4508–4511. (b) Clarke, D. G.; Crombie, L.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1007–1015. (c) Heyns, K.; Hohlweg, R. *Chem. Ber.* **1978**, *111*, 1632–1645.

(26) (a) Martin, J.; Parker, W.; Raphael, R. A. *J. Chem. Soc.* **1964**, 289–295. (b) Martin, J.; Parker, W.; Shroot, B.; Stewart, T. *J. Chem. Soc. C* **1967**, 101–108. (c) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1989–1997. (d) Welch, S. C.; Walters, R. L. *J. Org. Chem.* **1974**, *39*, 2665–2673.

(27) (a) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 2502–2512. (b) Boeckman, R. K., Jr.; Bershas, J. P.; Clardy, J.; Solheim, B. *Ibid.* **1977**, 3632–3633.

Scheme IX



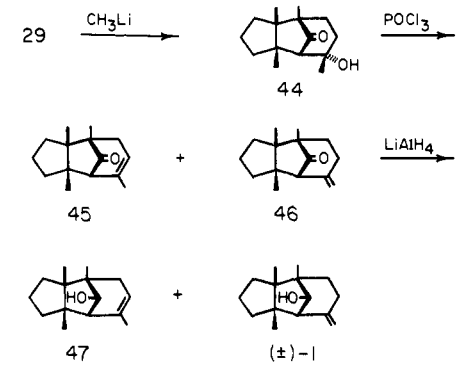
lactone reductive cyclizations.[26] The yield of diketone **29** from the enol lactone was 56%. Although this route to **29** required two additional steps, the overall yield was twice that obtained by the catalytic aldol cyclization.

It is of interest to consider briefly possible explanations for the remarkably efficient aldol cyclization (92% crude yield of ketol **5**) of the aluminum enolate presumably formed in the enol lactone reduction. It seems reasonable to assume that the reaction involves principally equilibration of the three aluminum alkoxides **40a**, **40b**, and **40c** (Scheme VIII, M = *i*-Bu_2Al).[30] Chelation between the carbonyl group and the metal in the aldol alkoxide has been considered to be an important thermodynamic factor in some metalloenolate aldol condensations.[26c,29] However, if the chelation involves an interaction of the metal with the nonbonded electrons of the carbonyl oxygen, the bridged chelate (**40d**) would be quite strained and may be regarded as a formal violation of Bredt's rule.[31]

Another thermodynamic driving force becomes evident upon consideration of changes in bond energies in the various equilibria. With the assumption that the bond strength of the Al–O bond is approximately the same in all three species, the following changes in bond energies (ΔBE) are estimated[32] for each equilibrium: **40a** ⇄ **40b** (ΔBE = −4 kcal/mol), **40a** ⇄ **40c** (ΔBE = −27 kcal/mol), and **40b** ⇄ **40c** (ΔBE = −23 kcal/mol). The large enthalpic driving force for formation of the ketol alkoxide (**40c**) arises mainly from the conversion of one C=C double bond in **40a** and **40b** to two C—C single bonds in **40c**. The exothermicity of the metalloenolate aldol condensation contrasts with a meager ΔBE of −5 kcal/mol for the simple catalytic aldol cyclization of **5** to **6** in which a strong C=O bond is lost.[32b] Thus, the enhanced driving force in the metalloenolate aldol condensation stems from the stoichiometric formation of the relatively high-energy enolate derivative (**40b**) of keto aldehyde **5**. It is to be expected, however, that, as the O—M bond becomes more ionic (e.g., M = K), the metallo enolate form **40b** will be stabilized with respect to **40a** and **40c** owing to delocalization of the negative charge.

Completion of the synthesis required regioselective methylenation of the cyclohexanone carbonyl and stereoselective reduction of the cyclopentanone carbonyl in diketone **29**. Although reactions

Scheme X



of **29** with organometallic reagents in fact occurred at C-5, it proved difficult to avoid a retro aldol ring opening. For example, α-phenylthio ketone **41** (55%) was the only product isolated from reaction of **29** with 1.5 equiv of ((phenylthio)methyl)lithium at −78 to −30 °C (Scheme IX). An attempt to incorporate the extra carbon by addition of methylmagnesium bromide to enol lactone **39** via the Fujimoto reaction[33] afforded diketone **33** (Scheme VI). It is not clear whether the failure of this reaction should be attributed to a less favorable cyclization equilibrium owing to steric interactions with the methyl group, competitive proton-transfer equilibrations which would generate other enolate anions, or a combination of both factors.

Another tactic tried was prior reduction of the bridged ketone (Scheme IX). The cyclohexanone carbonyl of **29** was first protected as its enolate anion[34] by deprotonation with 1 equiv of lithium diisopropylamide in THF at −78 °C, the remaining ketone was reduced with lithium aluminum hydride, and the excess hydride was consumed with gaseous ammonia. Unfortunately this procedure gave a 60:40 mixture of the epimeric keto alcohols **42** and **43**, in contrast to the high stereoselectivity observed in the reduction of gymnomitrone (**46**).[1]

Regioselective addition of 1 equiv of methyllithium to the cyclohexanone carbonyl group in ether at −78 °C followed by careful hydrolysis with aqueous ammonium chloride afforded ketol **44** (76%) as a single stereoisomer (Scheme X). Although no evidence is available on the stereochemistry of **44**, it seems very probable on steric grounds that the approach of the organolithium reagent occurred on the carbonyl face opposite to the trimethylene carbons. Dehydration of **44** to a 1:1 mixture of endo- and exocyclic β,γ-enones (**45** and **46**; 64%) was accomplished with phosphorous oxychloride in refluxing pyridine.[35] The mixture of ketones was reduced with lithium aluminum hydride, and the resulting alcohols were separated by preparative thin-layer chromatography on silver nitrate-impregnated silica gel. The more polar component proved to be (±)-gymnomitrol (±)-**1**, the IR, NMR, and mass spectra of which are identical with the corresponding spectra of natural (+)-gymnomitrol.

Experimental Section

General Aspects. All melting points and boiling points are uncorrected. Spectra were recorded with the following instruments: Perkin-Elmer 237 and 267 IR spectrophotometers; Varian EM-390, HA-100, and HR-220 NMR spectrometers; Varian CH-5 and 731 mass spectrometers. Elemental analyses were performed by the University of Illinois Microanalytical Laboratory.

Tetrahydrofuran (THF), diethyl ether, and 1,2-dimethoxyethane, when used as solvents for reactions, were freshly distilled from sodium–benzophenone ketyl. Dimethylformamide was distilled from calcium hydride. Diisopropylamine and hexamethyldisilazane were stored over 4A molecular sieves, and pyridine was kept over potassium hydroxide

(28) (a) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; Pergamon Press: Oxford, England, 1969; p 288. (b) Hassner, A.; Heathcock, C. H. *J. Org. Chem.* **1964**, *29*, 1350–1355.

(29) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310–3324.

(30) Since the major, if not exclusive, product is the axial ketol **5**, the reaction may well be kinetically controlled with respect to the stereochemistry at the carbinyl center (C-5).

(31) (a) The absence of intramolecular hydrogen bonding in bridged ketols similar to **5** indicates that the hydroxyl and carbonyl groups are remote from each other. See ref 26b and Eglinton, G.; Martin, J.; Parker, W. *J. Chem. Soc.* **1965**, 1243–1251. (b) Chelation may be important in stabilizing the aldol alkoxide if a molecule of THF is either interposed between the metal and the carbonyl carbon or coordinated to the carbonyl carbon from the equatorial direction. In this solvate the carbonyl group would resemble a hemiketal and chelation could then occur across the 1,3-diaxial oxygen atoms.

(32) (a) Bond energies were obtained from Streitwieser, A., Jr.; Heathcock, C. H. "Introduction to Organic Chemistry"; Macmillan Publishing Co.: New York, 1976; p 1187. (b) The strain energy associated with the tricyclic ring system[24] has not been included in the estimates of ΔBE for the equilibria.

(33) (a) Fujimoto, G. I. *J. Am. Chem. Soc.* **1951**, *73*, 1856. (b) Fujimoto, G. I.; Zwahlen, K. D. *J. Org. Chem.* **1960**, *25*, 445–447. (c) Weill-Raynal, J. *Synthesis* **1969**, *49*–56.

(34) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Wiltshire, C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1075–1079.

(35) Johnson, W. S.; Korst, J. J.; Clement, R. A.; Dutta, J. *J. Am. Chem. Soc.* **1960**, *82*, 614–622.

pellets. All reactions involving organometallic reagents or enolate anions were carried out under an atmosphere of dry nitrogen. The apparatus used for anhydrous reactions was dried in an oven at 130 °C for at least 3 h. All reaction temperatures were measured externally in the cooling bath used.

Column chromatographic purifications were performed with gravity flow using silica gel of particle size 0.05–0.2 mm purchased from Brinkman Instruments. Fractions of 1–25 mL were taken with a fraction collector and analyzed by thin-layer chromatography (TLC). Preparative TLC was carried out on Merck PF-254 silica gel plates. Gas chromatographic analyses were conducted with the following columns: (A) 1.2 m × 1 cm column packed with 15% FFAP (Free Fatty Acid Phase) on 60–80 mesh, acid-washed, dichlorodimethylsilane-treated Chromosorb W; (B) 1.8 m × 1 cm column packed with 20% SE-30 on 60–80 mesh Chromosorb W; (C) 3 m × 0.6 cm column packed with 20% SE-30 on 60–80 mesh Chromosorb W; (D) 1.8 m × 0.32 cm column packed with 3% OV-17 on 60–80 mesh Chromosorb W.

Tetramethyl (3aα,6aα)-octahydro-3a,6a-dimethyl-2,5-dioxo-1,3,4,6-pentalenetetracarboxylate was prepared by the procedure of Weiss and Edwards.[12] The pH of a solution of 174.2 g (1 mol) of dimethyl acetone-1,3-dicarboxylate and 47 g (0.55 mol) of 2,3-butanedione in 1 L of water was adjusted to 4.5 by addition of ca. 5 mL of 2 N sodium hydroxide, and the solution was stirred at room temperature for 3 days. The solid was filtered, washed with several portions of water, and dried. The yield was 163 g (82%) of the tetraester as a colorless solid, mp 153–155 °C (lit.[12] 144–146, 147–150 °C).

(3aα,6aα)-Tetrahydro-3a,6a-dimethyl-2,5(1*H*,3*H*)-pentalenedione (8). A solution of 163 g (0.41 mol) of the preceding tetraester in 250 mL of glacial acetic acid and 40 mL of water was heated at reflux under nitrogen for 7 h at which time the evolution of carbon dioxide had stopped. The mixture was cooled, and ca. 230 mL of solvent was evaporated under reduced pressure. The remaining solution was diluted with 100 mL of water, neutralized with sodium bicarbonate, and extracted with three 200-mL portions of ether. The combined extracts were washed with saturated sodium chloride and dried (Na_2SO_4). Concentration of the filtrate and cooling furnished 47.23 g (69.5%) of diketone **8**, mp 220–221 °C (lit.[12] 167–169 °C, 158–180 °C). The reason for the discrepancy in melting points is not clear.

(3aα,6aα)-5-Chloro-3,3a,6,6a-tetrahydro-3a,6a-dimethylpentalen-2-(1*H*)-one (9) was prepared in a manner similar to a literature procedure.[13] To a stirred solution of 144 g (0.68 mol) of diketone **8** in 500 mL of chloroform at 0 °C under nitrogen was added 50 g (0.24 mol) of phosphorus pentachloride. The ice bath was removed and the suspension stirred for 4.0 h at 22 °C. The resulting solution was cooled to 0 °C, and 200 mL of water was added. The organic layer was washed with successive portions of cold 20% sodium hydroxide until the aqueous layer remained colorless and then with saturated sodium chloride. The chloroform solution was dried ($MgSO_4$) and evaporated. The residue was recrystallized twice from cold hexane in order to recover the unreacted diketone. The diketone was then recycled with additional phosphorous pentachloride (0.35 equiv) and proportionally less chloroform. The hexane mother liquor containing the vinyl chloride **9** was washed again with 20% sodium hydroxide and saturated sodium chloride, dried ($MgSO_4$), and evaporated. Five of such reaction cycles provided 47.4 g (38%) of monovinyl chloride **9** (containing a trace of the divinyl chloride **10**) and 10.8 g (9.5%) of unreacted diketone. Preparative GC (column A, 160 °C) furnished the analytical sample of monovinyl chloride **9** as a colorless oil: IR (film) ν_{max} 1735 (C=O), 1620 cm^{-1} (C=C); ^1H NMR (CCl_4) δ 1.12 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.92–2.74 (m, 6 H, $CH_2C(O)CH_2$ and $CH_2C(Cl)$=CH), 5.50–5.75 (m, 1 H, CH=CCl). Divinyl chloride **10** was obtained as a colorless solid: mp 35–47 °C; IR (KBr) ν_{max} 1635 (C= C) cm^{-1}; ^1H NMR (CCl_4) δ 1.04–1.67 (m, 6 H, CH_3), 2.43–3.10 (m, 4 H, CH_2C=C), 5.35–5.48 (m, 2 H, C=CH).

Anal. Calcd for $C_{10}H_{13}ClO$: C, 65.04; H, 7.10. Found: C, 64.80; H, 7.08.

Anal. Calcd for $C_{10}H_{12}Cl_2$: C, 59.14; H, 5.96. Found: C, 59.12; H, 5.88.

(3aα,6aα)-Hexahydro-3a,6a-dimethyl-2-(1*H*)-pentalenone (7). Method A. A suspension of 13.9 g (77 mmol) of monovinyl chloride **9**, 18.5 g (0.15 mol) of anhydrous sodium acetate, and 7.0 g of 5% palladium on carbon in 400 mL of methanol was hydrogenated on a low pressure Parr hydrogenation apparatus for 16 h at 22 °C and 50 psi hydrogen in a manner similar to a literature procedure.[14] The reaction mixture was diluted with hexane, filtered, washed with water and saturated sodium chloride, dried ($MgSO_4$), and evaporated at 20 °C. After removal of a trace of octahydro-3a,6a-dimethylpentalene at reduced pressure (0.05 mm), there remained 7.55 g (65%) of ketone **7** as a colorless solid, which required no further purification, mp (sealed tube) 158–159 °C.

Method B. A 47-mL (0.102-mol) aliquot of 2.17 M *n*-butyllithium in hexane was added to a solution of 21.4 mL (0.1 mol) of hexamethyldisilazane in 30 mL of THF at −78 °C. After 5 min the dry-ice bath was replaced by an ice-water bath, and the solution was allowed to stir for 15 min. The solution of lithium hexamethyldisilazide thus prepared was slowly added to a suspension of 16.6 g (0.1 mol) of diketone **8** in 200 mL of THF which was stirred and cooled at −78 °C. After 15 min 15 mL (0.1 mol) of diethyl chlorophosphate was added to the yellow solution and the cooling bath was removed. After 2.5 h the pale yellow reaction mixture was diluted with 250 mL of 1:1 ether–pentane and poured into 300 mL of ice-cold saturated sodium bicarbonate. The aqueous layer was extracted with two portions of 1:1 ether–pentane. The combined organic layers were washed with 200 mL of ice-cold 1.2 N hydrochloric acid and saturated sodium chloride and dried by filtering through a cone of anhydrous sodium sulfate. This procedure was repeated with another 16.6 g (0.1 mol) of diketone **8**. Concentration of the combined, dried filtrate furnished 61.1 g of enol phosphate **11** as a yellow oil, which was used in the next step without further purification. The spectral properties of the product are as follows: IR (neat) ν_{max} 2960, 1745, 1660, 1280 cm^{-1}; ^1H NMR (CCl_4) δ 1.13 (s, 6 H, 2 CH_3), 1.31 (t, 6 H, J = 7 Hz, CH_3CH_2O); 1.8–2.6 (m, 6 H), 4.01 (dq, 4 H, J = 8, 7 Hz, CH_3CH_2O), 5.04 (br s, 1 H, vinyl H). A solution of 61.1 g of the enol phosphate in 300 mL of ethyl acetate was cooled at 0 °C and maintained under a blanket of nitrogen as 4.0 g of 5% platinum on carbon was carefully added. The suspension was hydrogenated on a Parr apparatus at room temperature with an initial charge of 73 psi of hydrogen. After 2 h when further absorption of hydrogen had ceased, the catalyst was removed by filtration through celite, the filtrate was diluted with 200 mL of 1:1 ether–pentane, and 300 mL of 7% sodium bicarbonate was slowly added. The aqueous layer was extracted twice with ether–pentane. The combined organic layers were washed with 7% sodium bicarbonate and saturated sodium chloride and dried (Na_2SO_4). Concentration of the filtrate and sublimation of the residue at 65–75 °C (0.35 mm) afforded 23.5 g (77%) monoketone **7** as a white solid: mp 159–160 °C (sealed tube); IR (CCl_4) ν_{max} 2950, 1750 cm^{-1}; ^1H NMR (CCl_4) δ 1.03 (s, 6 H, 2 CH_3), 1.69 (br s, 6 H, $CH_2CH_2CH_2$), 2.08 (ABd, 4 H, J = 17 Hz, CH_2C=O).

(3aα,6aα)-1-Formylhexahydro-3a,6a-dimethyl-2(1*H*)-pentalenone (12). A suspension of 6 g (50% in mineral oil, 0.125 mol) of sodium hydride in 160 mL of THF was stirred at room temperature under nitrogen as a solution of 5.22 g (0.035 mol) of monoketone **7** in 10 mL of THF and 10 mL (0.124 mol) of ethyl formate were added in succession.[36] Stirring was continued for 14 h after which the excess sodium hydride was destroyed by dropwise addition of 2 N sodium hydroxide. The mixture was poured into 2 N sodium hydroxide and extracted with two 50-mL portions of pentane to remove the mineral oil. The combined pentane layers were washed with 2 N sodium hydroxide. The combined aqueous layers were neutralized with concentrated hydrochloric acid and extracted three times with 1:1 ether–pentane. The organic layers were combined, washed with saturated sodium chloride, and dried (Na_2SO_4). Concentration of the filtrate yielded 5.3 g (83%) of the α-formyl ketone as a light brown solid, mp 87–89 °C. Sublimation at 50–55 °C (0.1 mm) furnished the analytical sample as a colorless solid: IR (KBr) ν_{max} 3300 (br, OH), 2950, 1690, 1605 cm^{-1}; ^1H NMR (CCl_4) δ 1.03, 1.13 (2 s, 6 H, 2 CH_3), 1.50–1.82 (m, 6 H, $CH_2CH_2CH_2$), 2.32 (ABd, 2 H, J = 18 Hz, CH_2CO), 7.22 (s, 1 H, C=C*H*OH), 10.66 (s, 1 H, OH).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.08; H, 8.74.

(1α,3aα,6aα)-Hexahydro-1,3a,6a-trimethyl-1-(2-propenyl)-2(1*H*)-pentalenone (14a). Method A. A solution of 0.62 g (3.4 mmol) of α-formyl ketone **12**, 0.32 g (3.5 mmol) of *n*-butyl mercaptan, and ca. 5 mg of *p*-toluenesulfonic acid hydrate in 20 mL of benzene was heated at reflux for 18 h using a Dean–Stark trap to collect the water formed.[16] The solution was cooled, diluted with benzene, washed with saturated sodium bicarbonate and saturated sodium chloride, dried ($MgSO_4$), and evaporated. Kugelrohr distillation at 140–180 °C (0.1–0.3 mm) provided 0.69 g (84%) of the (*n*-butylthio)methylene ketone **13a** as a pale yellow oil: IR (film) ν_{max} 1580 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 1.02 (br, t, ~3 H, J = ~4 Hz, CH_2CH_3), 1.04, 1.16 (2 s, 6 H, 2 CH_3), 1.32–1.97 (m, 6 H, $CH_2CH_2CH_2$), 2.15 (ABd, 2 H, CH_2CO), 2.82 (t, 2 H, J = 7 Hz, SCH_2), 7.15 (s, 1 H, C=CH).

The reduction–alkylation was carried out according to a literature procedure.[17] To a stirred solution of 35 mg (5.0 mmol) of lithium in 75 mL of liquid ammonia and 50 mL of dry 1,2-dimethoxyethane at −33 °C under nitrogen was added a solution of 0.52 g (2.0 mmol) of the (*n*-butylthio)methylene ketone **13a** and 72 mg (4.0 mmol) of water in 2.0 mL of 1,2-dimethoxymethane. After 0.5 h at −33 °C, allyl bromide was added (dropwise until the blue color was discharged, then another 1.21 g (10 mmol)). The ammonia was allowed to evaporate, and after 4 h the resulting mixture was diluted with water and extracted with ether. The

(36) Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1968**, *27*, 1620–1627.

ethereal extract was dried ($MgSO_4$) and evaporated. The remaining orange oil was purified by chromatography on 100 g of silica gel with 2% ethyl acetate in hexane as eluant. A middle fraction provided 200 mg (48%) of ketone **14a** as a pale yellow oil. In other runs, the yields ranged from 26 to 49%. Analysis by GC (column C, 165 °C) indicated that ca. 10% of unalkylated ketone was present. Preparative GC (column B, 150 °C) gave the analytical sample as a colorless oil: IR (film) ν_{max} 1740 (C=O), 1640 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 0.84, 0.96, 1.24 (3 s, 9 H, 3 CH_3), 1.32–1.82 (m, 6 H, $CH_2CH_2CH_2$), 1.85–2.46 (m, 4 H, CH_2CO and $CH_2CH{=}CH_2$), 4.87–5.12 (m, 2 H, $CH_2CH{=}CH_2$), 5.39–5.78 (m, 1 H, $CH_2CH{=}CH_2$).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.76. Found: C, 81.26; H, 10.55.

Method B. The α-(phenylthio)methylene ketone (**13b**) was prepared as described above for the (*n*-butylthio)methylene ketone **13a**, substituting thiophenol for *n*-butyl mercaptan. The reaction of 3.00 g (17 mmol) of α-formyl ketone **12** and 2.2 g (20 mmol) of thiophenol provided, after Kugelrohr distillation at 210–225 °C (0.1–0.5 mm), 4.26 g (94%) of **13b** as a pale yellow oil which apparently was a 4:1 mixture of *E* and *Z* isomers: IR (film) ν_{max} 1740 (C=O), 1650 (C=C), 1590 cm^{-1}; ^1H NMR (CCl_4) δ 1.06, 1.26 (2 s, 6 H, 2 CH_3), 1.4–2.0 (m, 6 H, $CH_2CH_2CH_2$), 2.22 (ABd, 2 H, CH_2CO), 7.1–7.65 (m, 6 H, C_6H_5 and C=CH). The following absorptions in the NMR spectrum are attributed to the *Z* isomer: δ 1.05, 1.12 (2 s, ca. 1.5 H, 2 CH_3), 6.68 (s, ca. 0.2 H, =CH).

Reduction–alkylation of **13b** according to the procedure above gave **14a** in 31–42% yield.

(3aα,6aα)-Hexahydro-1,1,3a,6a-tetramethyl-2(1*H*)-pentalenone (14b). The reduction–alkylation of 196 mg (0.72 mmol) of (phenylthio)methylene ketone **13b**, 27 mg (1.44 mmol) of water, 35 mg (5.0 mmol) of lithium, and 1.5 g (10.5 mmol) of methyl iodide in 20 mL of ammonia and 15 mL of dry THF, in the manner described for the preparation of ketone **14a**, yielded 76 mg (58%) of ketone **14b** as an oily solid. Sublimation at 90 °C (0.10 mm) furnished the analytical sample as a colorless solid: mp 138–140 °C; IR (KBr) ν_{max} 1740 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 0.91, 0.93, 0.96, 1.18 (4 s, 12 H, 4 CH_3), 1.37–1.88 (m, 6 H, $CH_2CH_2CH_2$), 2.18 (ABd, 2 H, CH_2CO).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.76; H, 11.09.

(1α,3aα,6aα)-Hexahydro-1-(methyl-d_3)-1,3a,6a-trimethyl-2(1*H*)-pentalenone (14c). The reaction of 4.8 g (17.6 mmol) of (phenylthio)-methylene ketone **13b**, 635 mg (35.2 mmol) of water, 350 mg (50 mmol) of lithium, and 7.7 g (53 mmol) of trideuteriomethyl iodide in 100 mL of ammonia and 60 mL of dry tetrahydrofuran, in the manner described for the preparation of ketone **14a**, afforded 1.92 g (41%) of ketone **14c** as a colorless oil. Preparative GC (column B, 100 °C) provided the pure sample as a colorless solid: mp 146–148 °C; ^1H NMR (CCl_4) δ 0.91, 0.93, 1.18 (3 s, 9 H, 3 CH_3).

Europium Shift Reagent Study with Deuterium-Labeled Alcohols 15a and 15b. Reduction of 300 mg of the trideuterio ketone **14c** with excess sodium borohydride in ethanol afforded a mixture of the two alcohols which were separated by column charomatography on 20 g of silica. Elution with 10–15% diethyl ether in hexane provided 55.2 mg of alcohol **15a** as a colorless solid: mp 135–138 °C; IR (KBr) ν_{max} 3325 (OH) cm^{-1}; ^1H NMR (CCl_4) δ 0.80, 0.95, 1.00 (3 s, 9 H, 3 CH_3), 1.05–2.36 (m, 9 H, $CH_2CH_2CH_2$, CH_2CHOH) 3.67–3.77 (m, 1 H, CHOH).

Further elution with 15–20% diethyl ether in hexane afforded 174.5 mg of alcohol **15b** as a colorless solid: mp 157–158 °C; IR (KBr) ν_{max} 3325 (OH) cm^{-1}; ^1H NMR (CCl_4) δ 0.82, 0.87, 1.02 (3 s, 9 H, 3 CH_3), 1.36–1.90 (m, 8 H, $CH_2CH_2CH_2$, CH_2CHOH), 3.72–3.89 (m, 1 H, CHOH).

NMR spectra of **15a** (0.30 mmol) and **15b** (0.94 mmol) in 0.5 mL 0.075 mL of carbon tetrachloride, respectively, were recorded as 50 μL aliquots of 0.111 M $Eu(fod)_3$ in carbon tetrachloride were added. The chemical shifts for the methyl groups were plotted as a function of the mole ratio $Eu(fod)_3$/ROH, and the slopes were determined.[18] The gradients were as follows: **15a**, 18.46 (δ_0 0.95, CH_3 at C-1), 6.46 and 5.38 (CH_3 at C-3a and C-6a); **15b**, 14.58 (δ_0 0.87, CH_3 at C-1), 6.42 and 6.08 (CH_3 at C-3a and C-6).

(1α,3aα,6aα)-Octahydro-3a,6a-dimethyl-2-oxopentalene-1-nitrile (16). A solution of 3.6 g (52 mmol) of hydroxylamine hydrochloride and 5.3 g (29.5 mmol) of α-formyl ketone (**12**) in 10 mL of methanol was added to a solution of sodium methoxide freshly prepared from 5.2 g (0.226 mol) of sodium and 200 mL of methanol under nitrogen.[37] The reaction mixture was heated at reflux for 20 h, cooled, and concentrated to a volume of ca. 100 mL at reduced pressure. The remaining solution was neutralized with 1.2 M hydrochloric acid and extracted with ether. The combined ether extracts were washed with aqueous sodium chloride, dried (Na_2SO_4), and concentrated. The residue was passed through a short column prepared from 60 g of silica gel using 30% ethyl acetate–hexane as eluant. Evaporation of the eluate afforded 4.65 g (89%) of the pale yellow α-cyano ketone (**16**), mp 128–135 °C (dec), as a 60:40 mixture of isomers. Sublimation at 100 °C (0.1 mm) gave the analytical sample: IR (CCl_4) ν_{max} 3300, 2960, 2200, 1750 cm^{-1}; ^1H NMR (CCl_4) δ 1.11, 1.13, 1.17, and 1.20 (4 s, 6 H, 4CH_3), 1.4–2.0 (m, 6 H, $CH_2CH_2CH_2$), 2.30 (ABd, 2 H, CH_2CO), 3.13 and 3.20 (2 s, 1 H, CHCN).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.46; H, 8.55; N, 7.73.

(1α,3aβ,6aβ)-Octahydro-3a,6a-dimethyl-2-oxo-1-(2-propenyl)pentalene-1-nitrile (18). A 0.88-g (5.0-mmol) portion of a 22% mineral oil suspension of potassium hydride was washed several times with dry 1,2-dimethoxyethane under nitrogen in order to remove the mineral oil and then suspended in 40 mL of 1,2-dimethoxyethane. To this suspension was added 0.776 g (4.38 mmol) of α-cyano ketone (**16**) in 2 mL 1,2-dimethoxyethane, dropwise over a period of 2 min. The mixture was stirred for 10 min, and then 0.85 g (7.0 mmol) of allyl bromide was added in one portion. The resulting mixture was stirred overnight at room temperature, acidified with 10% hydrochloric acid, and extracted with ether. The ethereal extract was washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on 25 g of silica gel, with 5% ether in hexane as eluant, providing 0.717 g (77%) of the allyl enol ether **17** as a pale yellow oil: IR (film) ν_{max} 2100 (C≡N), 1630 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 1.06, 1.14 (2 s, 6 H, 2 CH_3), 1.22–2.26 (m, 6 H, $CH_2CH_2CH_2$), 2.42 (s, 2 H, $CH_2C(O)$=C), 4.73–4.86 (m, 2 H, $CH_2CH{=}CH_2$), 5.17–5.60 (br d, 2 H, J = 6 Hz, $CH_2CH{=}CH_2$), 5.72–6.36 (m, 1 H, $CH_2CH{=}CH_2$).

A solution of 717 mg (3.37 mmol) of enol ether **17** in 1 mL of benzene was sealed in a glass tube under vacuum and heated at 122 °C overnight. The cooled tube was opened, the solvent was evaporated, and the resulting orange oil was purified by chromatography on 15 g of silica gel. Elution with 10:1 and 3:1 hexane–ether afforded 498 mg (70%) of the α-cyano ketone (**18**) as a yellow, oily solid. Preparative GC (column A, 180 °C) provided the analytical sample as a colorless solid: mp 71–73 °C; IR (KBr) ν_{max} 2130 (C≡N), 1755 (C=O), 1650 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 1.16, 1.25 (2 s, 6 H, 2 CH_3), 1.52–2.16 (m, 6 H, $CH_2CH_2CH_2$), 2.37 (s, 2 H, CH_2CO), 2.48 (d, 2 H, J = 5 Hz, $CH_2CH{=}CH_2$), 5.02–5.27 (m, 2 H, $CH_2CH{=}CH_2$), 5.60–7.04 (m, 1 H, $CH_2CH{=}CH_2$).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.57; H, 8.87; N, 6.35.

(1α,3aβ,6aβ)-Hexahydro-1,3a,6a-trimethyl-1-(2-propenyl)-2(1*H*)-pentalenone (19). To a solution of 91 mg (13 mmol) of lithium in 100 mL of liquid ammonia and 60 mL of dry THF at −33 °C under nitrogen was added a solution of 1.00 g (4.70 mmol) of α-cyano ketone **18** in 3 mL of 1,2-dimethoxyethane. The solution was stirred at −33 °C for 5 min after which the blue color was discharged by adding 1.2 mL of methyl iodide. Another 1.95 g (13.7 mmol) of methyl iodide in 100 mL of THF was added, the ammonia was allowed to evaporate, a further 1.42 g (10 mmol) of methyl iodide was added, and the resulting white suspension was stirred overnight at room temperature. The reaction mixture was diluted with water and extracted with ether. The combined ethereal extracts were washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated. Chromatography of the residue on 60 g of silica gel with 5% ether in hexane as eluant provided 552 mg (58%) of ketone **19** as a pale yellow oil. Although the product from this and several other runs was homogeneous according to TLC analysis, it was in fact usually contaminated with a substantial amount of a byproduct which was probably the unalkylated α-allyl ketone. The byproduct was readily separated after lithium aluminum hydride reduction by column chromatography (see below). It was found subsequently that improved yields in the reduction–alkylation of α-cyano ketones are obtained by quenching excess lithium with 3-hexyne and evaporating all of the ammonia before adding a THF solution of the alkyl halide (see procedure for the preparation of enol silane **37**). Preparative GC (column A, 160 °C) gave the analytical sample as a colorless oil: IR (film) ν_{max} 1740 (C=O), 1640 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 0.98, 1.03, 1.18 (3 s, 9 H, 3 CH_3), 1.30–1.86 (m, 6 H, $CH_2CH_2CH_2$), 1.96–2.27 (m, 4 H, CH_2CO and $CH_2CH{=}CH_2$), 4.78–5.23 (m, 2 H, $CH_2CH{=}CH_2$), 5.62–6.34 (m, 1 H, $CH_2CH{=}CH_2$).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.31; H, 10.81.

(1α,2aβ,3aα,6aα)-Octahydro-1,3a,6a-trimethyl-2-(phenylmethoxy)-1-(2-propenyl)pentalene (20). A solution of 2.2 g (10.7 mmol) of ketone **14a** in 10 mL of dry THF was added to a suspension of 760 mg (20 mmol) of lithium aluminum hydride in 100 mL of dry THF at room temperature under a nitrogen atmosphere. The suspension was stirred for 0.5 h, the excess hydride was destroyed by dropwise addition of ethanol, and the mixture was acidified with 10% hydrochloric acid. The solution was diluted with water and extracted with ether. The ethereal

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extract was washed with saturated sodium bicarbonate and saturated sodium chloride, dried ($MgSO_4$), and evaporated. Chromatography of the resulting oil in 100 g of silica gel with 10% ether in hexane as eluant furnished 2.17 g (98%) of a 55:45 mixture of isomeric alcohols as a colorless oil: IR(film) ν_{max} 3380 (OH), 1640 (C=C) cm^{-1}.

The benzyl ether was prepared in a manner similar to a literature procedure.[38] A solution of 2.17 g (10.3 mmol) of the alcohols in 10 mL of dry THF was added dropwise to a 2.5-g (15 mmol) portion of a 23% mineral oil suspension of potassium hydride in 100 mL of 1,2-dimethoxyethane at room temperature under nitrogen. The suspension was stirred for 10 min, 1.77 g (10.3 mmol) of benzyl bromide was added in one portion, and the resulting mixture was stirred for 18 h at room temperature. The reaction mixture was carefully diluted with 10% hydrochloric acid and extracted with ether. The ethereal extract was washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated. Chromatography of the product on 100 g of silica gel with 5% ether in hexane as eluant gave 2.7 g (88%) of the liquid benzyl ether **20** as a 55:45 mixture of epimers (by NMR). Preparative GC furnished the analytical sample: IR (film) ν_{max} 1640 (C=C), 735, 695 (benzyl) cm^{-1}; ^1H NMR (CCl_4) δ 0.82, 0.90, 1.01 and 0.85, 0.90, 0.92 (6 s, 9 H, 6 CH_3 for the two isomers), 1.14–2.02 (m, 8 H, $CH_2CH_2CH_2$, CH_2CHOCH_2), 2.23 (d, 2 H, J = 3 Hz, $CH_2CH{=}CH_2$), 3.20–3.81 (m, 1 H, CH_2CHOCH_2), 4.48 (ABd, 2 H, $OCH_2C_6H_5$), 4.75–5.25 (m, 2 H, $CH_2CH{=}CH_2$), 5.54–6.20 (m, 1 H, $CH_2CH{=}CH_2$), 7.18–7.45 (br s, 5 H, C_6H_5).

Anal. Calcd for $C_{21}H_{30}O$: C, 84.51; H, 10.13. Found: C, 84.26; H, 10.03.

(1α,2αβ,3aα,6aα)-1-[2-(1,3-Dioxolan-2-yl)ethyl]octahydro-1,3a,6a-trimethyl-2-(phenylmethoxy)pentalene (21). A solution of 2.7 g (9.1 mmol) of benzyl ether **20** in 50 mL of dry THF was stirred and cooled at 0 °C under a nitrogen atmosphere as a 20-mL portion (20 mmol) of 1.0 M borane in THF was added.[39] After 18 h at room temperature, 20 mL of 10% sodium hydroxide and 15 mL of 30% hydrogen peroxide were added, and the reaction mixture was stirred vigorously for an additional 0.5 h. The mixture was diluted with water and extracted with diethyl ether. The ethereal extract was washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on 60 g of silica gel. Elution with 10–20% ether in hexane afforded 2.0 g (70%) of the hydroxy ether as a colorless oil: IR (film) ν_{max} 3340 (OH) cm^{-1}; ^1H NMR (CCl_4) δ 0.85, 0.90, 0.96 and 1.02, 1.04, 1.17 (6 s, 9 H, 6 CH_3, isomer ratio 55:45), 1.19–2.12 (m, 12 H, $CH_2CH_2CH_2$, CH_2CHOCH_2, $CH_2CH_2CH_2OH$), 2.96 (br s, 1 H, OH), 3.22–3.85 (m, 3 H, CH_2OH, $CHOCH_2$), 7.23 (br s, 5 H, C_6H_5).

A solution of 2.0 g (6.3 mmol) of the above alcohol in 10 mL of dichloromethane was added to a stirred solution of 100 mmol of chromium trioxide–dipyridine complex in 70 mL of dichloromethane.[40] After 0.5 h at room temperature, the mixture was diluted with ether and filtered. The ethereal filtrate was washed successively with several portions of 10% sodium hydroxide, 10% hydrochloric acid, and saturated sodium chloride, dried ($MgSO_4$), and evaporated. Purification of the residue by chromatography on 50 g of silica gel with 10% ether in hexane as eluant provided 1.69 g (86%) of the benzyloxy aldehyde as a colorless oil: IR (film) ν_{max} 2710, 1720 (CHO)cm^{-1}; ^1H NMR (CCl_4) δ 0.84, 0.88, 0.92, 1.01, 1.05, 1.14 (6 s, 9 H, 6 CH_3 in 2 isomers), 1.20–2.19 (m, 10 H, $CH_2CH_2CH_2$, CH_2CH_2CHO, CH_2CHOCH_2), 2.36 (t, 2 H, J = 7 Hz, CH_2CH_2CHO), 3.30–3.80 (m, 1 H, $CHOCH_2$), 4.37 (m, 2 H, $CHOCH_2$), 7.20 (br s, 5 H, C_6H_5), 9.59 (br s, ~1 H, CHO).

A solution of 1.69 g (5.4 mmol) of the above aldehyde, 0.64 g (10 mmol) of ethylene glycol, and a few milligrams *p*-toluenesulfonic acid hydrate in 50 mL of benzene was stirred and heated at reflux for 18 h, using Dean–Stark trap to collect the water. The solution was cooled, diluted with ether, washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated. Chromatography of the product on 60 g of silica gel with 10% ether in hexane as eluant afforded 1.64 g (87%) of the ketal ether (**21**) as a colorless oil: IR (film) no carbonyl band observed; ^1H NMR (CCl_4) δ 0.90, 1.00, 1.13 and 0.95, 1.03, 1.09 (6 s, 9 H, 6 CH_3, isomer ratio 55:45), 1.20–2.00 (m, 12 H, $CH_2CH_2CH_2$, $CH_2CH_2CH(O)_2$, CH_2CHOCH_2), 3.38 (d, 1 H, J = 7 Hz, $CHOCH_2$), 3.77 (m, 4 H, OCH_2CH_2O), 4.42, 4.46 (2 s, 2 H, $OCH_2C_6H_5$), 4.70 (t, 1 H, J = 5 Hz, $CH_2CH_2CH(OR)_2$), 7.22 (br s, 5 H, C_6H_5).

(1α,3aα,6aα)-1-[2-(1,3-Dioxolan-2-yl)ethyl]hexahydro-1,3a,6a-trimethyl-2(1*H*)-pentalenone (22). The following procedure for cleavage of the benzyl ether is based on one from the literature.[41] A solution of 175 mg (25 mmol) of lithium in 50 mL of liquid ammonia and 30 mL of dry THF was stirred and cooled at −33 °C under an atmosphere of nitrogen as a solution of 1.56 g (4.36 mmol) of benzyl ether **21** in 5 mL of dry tetrahydrofuran was added.[41] After 0.5 h, the blue color was discharged with 3-hexyne and the resulting yellow color was discharged with methanol. The ammonia was allowed to evaporate and the reaction mixture was diluted with water and extracted with ether. The ethereal extract was washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated. The residual oil was immediately oxidized with 50 mmol of chromium trioxide–dipyridine complex in 200 mL of dichloromethane for 0.5 h as described in the preceding procedure.[40] Purification of the crude product by chromatography on 60 g of silica gel with 10–25% ether in hexane as eluant provided 0.6 g (50%) of the keto acetal (**22**) as a colorless oil. Preparative GC (column A, 200 °C) furnished the analytical sample: IR (film) ν_{max} 1735 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 0.87, 0.98, 1.27 (3 s, 9 H, 3 CH_3), 1.10–1.84 (m, 10 H, $CH_2CH_2CH_2$, $CH_2CH_2CH(OR)_2$), 2.10 (ABd, 2 H, CH_2CO), 3.97 (m, 4 H, OCH_2CH_2O). 4.72 (m, 1 H, $CH(OR)_2$).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.17; H, 9.69.

(3aα,4β,8β,8aα)-Octahydro-3a,8,8a-trimethyl-4,8-methanoazulene-5,9(1*H*)-dione (25). A solution of 0.55 g (2.07 mmol) of the keto acetal **22** and 25 mL of 10% hydrochloric acid in 100 mL of acetone was stirred and heated at reflux for 2.5 h. The solution was cooled, diluted with water, and extracted with ether. The ethereal extract was washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated. Chromatography of the residual oil on 10 g of silica gel with 50% ether in hexane as eluant provided 0.45 g (97%) of tricyclic ketol **24** as a pale yellow oil: IR (film) ν_{max} 3450 (OH), 1740 (C=O) cm^{-1}.

A solution of 0.45 g (2.02 mmol) of ketol **24** in 20 mL of acetone was stirred as 6 N chromic acid was added dropwise until the red-orange color persisted.[42] The mixture was stirred for 10 min and then ethanol was added dropwise until the green color persisted. The resulting mixture was diluted with water and extracted with ether. The ethereal extract was washed with water, saturated sodium bicarbonate, and saturated sodium chloride, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on 88 g of silica gel. Elution with 20% ether in hexane afforded 254 mg (57%) of the bicyclic diketone **25** as a colorless solid. Sublimation at 50–80 °C (0.20 mm) furnished the analytical sample: mp (sealed tube) 214–216 °C; IR (KBr) ν_{max} 1740 (C=O), 1715 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04, 1.07, 1.10 (3 s, 9 H, 3 CH_3), 1.16–2.62 (m, 10 H, $CH_2CH_2CH_2$, CH_2CH_2CO), 3.00 (s, 1 H, C(O)CHCO).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.08; H, 8.95.

(1α,2αβ,3aβ,6aβ)-Octahydro-1,3a,6a-trimethyl-2-(phenylmethoxy)-1-(2-propenyl)pentalene (26). The reduction of 552 mg (2.65 mmol) of ketone **19** with lithium aluminum hydride in dry THF was performed in the manner described for the reduction of ketone **14a**. Chromatography of the product on 60 g of silica gel with 15% ether in hexane as eluant provided two fractions. The first fraction gave the alcohol resulting from the reduction of a byproduct (probably unalkylated ketone) which had been present as a contaminant in **19**. The second fraction gave 273 mg (49%) of a 90:10 diastereomeric mixture of the alcohols as a colorless oil: IR (film) ν_{max} 3400 (OH) cm^{-1}.

The benzylation of 273 mg (1.30 mmol) of the above alcohol with a 0.33-g (1.9-mmol) portion of a 23% mineral oil suspension of potassium hydride and 0.22 g (1.30 mmol) of benzyl bromide in 70 mL of dry THF in the manner described for the preparation of benzyl ether **21** furnished 366 mg (95%) of benzyl ether **26** as a colorless oil. Preparative GC (column B, 210 °C) gave the analytical sample as a single isomer: IR (film) ν_{max} 1640 (C=C), 735, 695 cm^{-1}; ^1H NMR (CCl_4) δ 0.84, 0.88, 1.01 (3 s, 9 H, 3 CH_3), 1.06-2.37 (m, 10 H, $CH_2CH_2CH_2$, $CH_2CH{=}CH_2$, CH_2CHOCH_2), 3.20–3.78 (m, 1 H, CH_2CHOCH_2), 4.32–4.58 (ABd, 2.H, CH_2CHOCH_2), 4.77–5.21 (m, 2 H, $CH_2CH{=}CH_2$), 5.53–6.38 (m, 1 H, $CH_2CH{=}CH_2$), 7.28 (br s, 5 H, C_6H_5).

Anal. Calcd for $C_{21}H_{30}O$: C, 84.51; H, 10.13. Found: C, 84.30; H, 9.97.

(1α,2αβ,3aβ,6aβ)-1-[2-(1,3-Dioxolan-2-yl)ethyl]octahydro-1,3a,6a-trimethyl-2-(phenylmethoxy)pentalene (27). The hydroboration, oxidation, and acetalization of 739 mg (2.48 mmol) of the benzyl ether **26** was carried out in the manner described for the conversion of **20** to **21** and gave, after chromatography on 60 g of silica gel, with 15% ether in hexane as eluant, 633 mg (71% overall) of benzyl ether **27** as a pale yellow oil. The overall yield for the conversion of ketone **19** to **27** ranged from 32 to 58%. Preparative GC (column B, 270 °C) furnished the analytical sample as a colorless oil: IR (film) no carbonyl band observed; ^1H NMR (CCl_4) δ 0.94, 0.98, 1.13 (3 s, 9 H, 3 CH_3), 1.15–2.06 (m, 12 H, $CH_2CH_2CH_2$, CH_2CHOCH_2, $CH_2CH_2CH(OR)_2$), 4.30 (d, 1 H, J =

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6 Hz, CH_2CHOCH_2), 3.75 (m, 4 H, OCH_2CH_2O), 4.46 (s, 2 H, $OCH_2C_6H_5$), 4.71 (t, 1 H, J = 5 Hz, $CH_2CH_2CH(OR)_2$), 7.23 (br s, 5 H, C_6H_5).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.23; H, 9.80.

(1α,3aβ,6aβ)-1-[2-(1,3-Dioxolan-2-yl)ethyl]hexahydro-1,3a,6a-trimethyl-2(1*H*)-pentalenone (28). Method A. The reductive cleavage of 457 mg (1.27 mmol) of benzyl ether **27** with lithium–ammonia, in the manner described for the isomeric benzyl ether **21**, provided, after chromatography on 10 g of silica gel, with a gradient of ether–hexane mixtures as eluant, 210 mg (62%) of the ketal alcohol as a colorless oil: IR (film) ν_{max} 3400 (OH) cm^{-1}.

The oxidation of 210 mg (0.79 mmol) of the preceding ketal alcohol in the manner described for the preparation of **22**, afforded, after chromatography on 10 g of silica gel, with 10% ether in hexane as eluant, 161 mg (77%) of keto acetal **28** as a pale yellow oil. Preparative GC (column A, 200 °C) furnished the analytical sample as a colorless oil: IR (film) ν_{max} 1740 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 0.93, 0.97, 1.10 (3 s, 9 H, 3 CH_3), 1.3–1.8 (m, 10 H, $CH_2CH_2CH_2$, $CH_2CH_2CH(OR)_2$), 2.08 (ABd, 2 H, J = 17 Hz, CH_2CO), 3.67 (m, 4 H, OCH_2CH_2O), 4.48 (m, 1 H, $CHC(OR)_2$); mass spectrum m/e (relative intensity) 252 (M^+, 5), 210 (21), 122 (6), 99 (10), 95 (9), 74 (100).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.16; H, 10.09.

Method B. A solution of 1.404 g (4.3 mmol) of enol silane **37** in 25 mL of THF was stirred and cooled at 0 °C as 6.6 mL (4.82 mmol) of 0.73 M methyllithium in ether was added. The cooling bath was removed, and 3 h later 3 mL (48 mmol) of methyl iodide was added. Stirring was continued for 17 h at room temperature at which time the reaction mixture was poured into 7% sodium bicarbonate and extracted with three 50-mL portions of 1:1 ether–pentane. The combined extracts were washed with saturated sodium chloride and dried (Na_2SO_4). The filtrate was concentrated, and the residue was purified by chromatography on 40 g of silica gel with 20% acetone–hexane as eluant. The yield of the keto acetal (**28**) was 0.749 g (65%). The IR and NMR spectra are identical with those of keto acetal prepared by method A.

(1α,3aβ,6aβ)-Hexahydro-1,3a,6a-trimethyl-1-(3-oxopropyl)-2(1*H*)-pentalenone (6). A solution of 1.13 g (4.25 mmol) of keto acetal **28** and 6 mL of 1.2 N hydrochloric acid in 15 mL of acetone was heated at reflux under nitrogen for 3 h. The mixture was cooled, poured into 7% sodium bicarbonate, and extracted with two 50-mL of 1:1 ether–pentane. The combined organic extracts were washed with saturated sodium chloride, dried (Na_2SO_4), and evaporated. The liquid keto aldehyde (0.975 g, 100%) was used without further purification. Preparative GC (column A, 200 °C) furnished the analytical sample as a colorless oil: IR (film) ν_{max} 2970, 2720, 1740 (sh), 1730 cm^{-1}; ^1H NMR (CCl_4) δ 0.98, 1.02, 1.19 (3 s, 9 H, 3 CH_3), 1.3–2.1 (m, 8 H), 2.19 (ABd, 2 H, J = 17 Hz, CH_2C=O), 2.4–2.9 (m, 2 H, CH_2CHO), 9.73 (br s, 1 H, CHO).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.35; H, 9.77.

(3aα,4α,8α,8aα)-Octahydro-3a,8,8a-trimethyl-4,8-methanoazulene-5,9(1*H*)-dione (29). Method A. A solution of 0.5 g of sodium carbonate in 100 mL of water was stirred at room temperature under nitrogen as a solution of 0.83 g (3.74 mmol) of keto aldehyde **6** in 75 mL of methanol was added. The resulting solution was stirred at room temperature under nitrogen for 3 days, diluted with water, and extracted with 3:1 ether–hexane. The organic extract was washed with water and saturated sodium chloride, dried ($MgSO_4$), and evaporated. The residual oil was purified by chromatography on 40 g of silica gel. Elution with 30% ether in hexane afforded 0.46 g (55%) of recovered keto aldehyde, which was recycled with additional sodium carbonate–water–methanol. Further elution with 75% ether in hexane gave 151 mg (18%) of **(3aα,4α,5α,8α,8aα)-decahydro-7-hydroxy-3a,4,8a-trimethyl-4,8-methanoazulen-9-one (5)** as a pale yellow oil. Three reaction cycles provided 298 mg (36%) of keto aldehyde **6** and 257 mg (31%) of ketol **5**. The spectral data for **5** are the same as those given below in method B.

When a solution of 17 mg (0.077 mmol) of ketol **5** and 12 mg of sodium carbonate in 3.0 mL of water and 3.0 mL of methanol was stirred for 1.5 days at room temperature and the product was isolated as above, 4.0 mg (23%) of keto aldehyde **6** and 10 mg (59%) of ketol **5** were recovered. The IR and NMR spectral data for the crude recovered keto aldehyde **6** were similar to those obtained for material prepared from hydrolysis of the keto acetal **28**.

A solution of 257 mg (1.16 mmol) of ketol **5** in 20 mL of acetone was oxidized in the manner described above for the isomeric ketol **24**.[42] Chromatography of the product on 10 g of silica gel, with 25% ether in hexane as eluant, furnished 141 mg (55%) of bridged diketone **29** as a colorless solid. Sublimation at 80–90 °C (0.05 mm) afforded the analytical sample: mp (sealed tube) 214–216 °C; melting point of a 1:1 mixture of diketones **25** and **29** at 204–207 °C. The spectral properties of **29** are given below.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.40; H, 9.03.

Method B. A solution of 0.152 g (0.69 mmol) of enol lactone **39** in 4 mL of THF was stirred and cooled at −78 °C under nitrogen as 0.7 mL (0.7 mmol) of 1 M diisobutylaluminum hydride in toluene was added.[26d] After 5 min the dry-ice bath was replaced by an ice–water bath. After 6 h 0.7 mL of 1.2 M hydrochloric acid was added. The mixture was poured into 1.2 M hydrochloric acid and extracted with two 30-mL portions of 1:1 ether–pentane. The combined extracts were washed with 7% sodium bicarbonate and saturated sodium chloride before drying (Na_2SO_4). Evaporation of the filtrate gave 0.138 g (90%) of ketol **5** which was used without further purification. The spectral characteristics of ketol **5** are as follows: IR (film) ν_{max} 3450 (OH), 2960, 1745 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 0.79, 0.83, 0.93 (3 s, 9 H, 3 CH_3), 1.2–2.3 (m, 11 H) 3.13 (br s, 1 H, OH), 4.33 (br t, $W_{1/2}$ = 11 Hz, 1 H, J = ~4.5 Hz, $CHOH$).

The oxidation of 138 mg (0.62 mmol) of ketol **5** with aqueous chromic acid in 4 mL of acetone was carried out as described in part A, and the product was isolated in a similar manner. Purification by preparative TLC using 30% ethyl acetate–pentane furnished 85 mg (62%) of diketone **29**: mp 214–216 °C; IR (CCl_4) ν_{max} 2960, 1745 (C=O), 1710 (C=O) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) δ 0.91, 1.01, 1.08 (3s, 9 H, 3 CH_3), 1.43–1.86 (m, 6 H, 3 CH_2), 2.00 (m, 2 H, CH_2), 2.48 (m, 2 H, CH_2CO), 2.95 (s, 1 H, H at C-4). The IR and NMR spectra of **29** are superimposable upon those of the nordiketone from natural gymnomitrol.[22]

(3aα,4β,8β,8aα)-Decahydro-7-hydroxy-3a,8a-dimethyl-9-oxo-4,8-methanoazulene-4-nitrile (30). A mixture of 133 mg (0.75 mmol) of α-cyano ketone **16**, 60 mg (1.05 mmol) of acrolein, and 1 pellet of potassium hydroxide in 5.0 mL of ethyl acetate was stirred for 19 h at room temperature.[43] Ether was added and the ethereal solution was washed with water, 10% hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, before drying with magnesium sulfate. The filtrate was evaporated and the residue was purified by chromatography on 8 g of silica gel. Elution with 75–100% ether in hexane afforded 95 mg (54%) of cyano ketol **30** as an oily solid. Three recrystallizations from ether gave the analytical sample as colorless needles: mp 198–203 °C; IR (KBr) ν_{max} 3435 (OH), 2250 (C≡N), 1745 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18, 1.23 (2 s, 6 H, 2 CH_3), 1.37–1.95 (m, 10 H), 2.78 (br s, 1 H, H at C-8), 4.47 (br s, $W_{1/2}$ = ~10 Hz, 1 H, $CHOH$).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.02; H, 8.21; N, 6.00. Found: C, 71.96; H, 8.34; N, 6.20.

(1α,3aβ,6aβ)-Octahydro-2-oxo-1-(3-oxobutyl)-3a,6a-dimethylpentalene-1-nitrile (31). A solution of 1.3 g (7.35 mmol) of α-cyano ketone **16**, 0.56 g (8.0 mmol) of methyl vinyl ketone, and 0.5 g (4.9 mmol) of triethylamine in 40 mL of benzene was stirred at room temperature for 8 d.[44] The solution was evaporated and the product was purified by filtration through silica gel. Elution with 20% ether in hexane furnished 1.10 g (61%) of cyano diketone **31** as a pale yellow oil. Preparative GC (column A, 250 °C) gave the analytical sample as a colorless oil: IR (film) ν_{max} 2230 (C≡N), 1740 (C=O), 1710 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 1.15, 1.31 (2 s, 6 H, 2 CH_3), 1.45–1.90 (m, 6 H, $CH_2CH_2CH_2$), 2.10 (s, 3 H, CH_3CO), 2.37 (ABd, 2 H, CH_2CO), 2.64 (m, 2 H, $CH_2C(O)CH_3$).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.77; H, 8.56; N, 5.82.

(1aα,3aβ,6aβ)-Hexahydro-1,3a,6a-trimethyl-1-(3-oxobutyl)-2(1*H*)-pentalenone (33). Method A. A solution of 741 mg (3.04 mmol) of cyano diketone **31**, 192 mg (3.1 mmol) of ethylene glycol, and a few milligrams of *p*-toluenesulfonic acid hydrate in 30 mL of benzene was heated at reflux for 10 h, using a Dean–Stark trap to collect the water. The solution was cooled and diluted with ether. The ethereal solution was washed with 10% sodium hydroxide and saturated sodium chloride, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on 20 g of silica gel. Elution with 30% ether in hexane afforded 667 mg (76%) of ketal (**32**) as a pale yellow oil. Purification of a sample by preparative GC (column A, 230 °C) gave a crystalline solid: mp 74–79 °C; IR (film) ν_{max} 2250 (C≡N), 1745 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 1.14, 1.23, 1.25 (3 s, 9 H, 3 CH_3), 2.33 (ABd, 2 H, CH_2CO), 3.85 (s, 4 H, OCH_2CH_2O).

To a stirred solution of 49 mg (7.0 mmol) of lithium in 60 mL of liquid ammonia at −78 °C under nitrogen was added a solution of 667 mg (2.30 mmol) of ketal **32** in 5.0 mL of dry THF. After addition of another 15 mL of THF, the solution was warmed to −33 °C for 0.5 h and then the blue color was discharged with 3-hexyne. A solution of 4.7 g (33 mmol)

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of methyl iodide was added, the ammonia was allowed to evaporate, and the resulting reaction mixture was stirred for 17 h at room temperature. The mixture was diluted with water and extracted with ether. The ethereal extract was washed with 10% hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, before drying ($MgSO_4$). Evaporation of the filtrate and chromatography of the residue on 10 g of silica gel, with 10–25% ether in hexane as eluant, yielded 281 mg (44%) of the keto ketal as a pale yellow oil.

A solution of 281 mg (1.01 mmol) of the keto ketal in 30 mL of acetone and 20 mL of 10% hydrochloric acid was heated at reflux for 1.0 h. The solution was cooled, diluted with water, and extracted with ether. The ethereal extract was washed with water, 10% sodium bicarbonate, and saturated sodium chloride, before drying ($MgSO_4$). The solvent was evaporated, and the residual oil was purified by chromatography on 10 g of silica gel. Elution with 40% ether in hexane furnished 207 mg (92%) of diketone **33** as a colorless oil. The NMR spectrum of the product shows the presence of an impurity which is very likely the unmethylated diketone. Preparative GC (column A, 120 °C) provided the analytical sample: IR (film) 1740 (C=O), 1720 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 0.98, 1.00, 1.20 (3 s, 9 H, 3 CH_3), 1.36–1.95 (m, 8 H), 2.08 (s, 3 H, CH_3CO), 2.10 (ABd, 2 H, CH_2CO), 2.60 (m, 2 H, $CH_2C(O)CH_3$).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.01; H, 10.14.

Method B. To an ice-cold solution of 44 mg (0.2 mmol) of enol lactone **39** in 4 mL of freshly distilled ether was added 0.07 mL (0.21 mmol) of 3.03 M methylmagnesium bromide in ether under nitrogen.[33] The ice bath was removed after 5 min, and the suspension was stirred for 17 h. The mixture was hydrolyzed with 0.5 mL of saturated ammonium chloride and diluted with 1:1 ether–pentane. The solution was added to saturated ammonium chloride, and the product was extracted with ether–pentane. The combined organic extracts were washed with saturated sodium chloride and dried (Na_2SO_4). The filtrate was evaporated, and the residue was purified by chromatography on 10 g of silica gel. Elution with 10% acetone–hexane furnished 17.8 mg of recovered enol lactone and 11.5 mg (41% based on unrecovered enol lactone) of diketone **33**. The IR and NMR spectra of the product match those of the diketone prepared by method A: mass spectrum, *m/e* (relative intensity) 236 (M^+, 9), 180 (11), 179 (13), 137 (11), 124 (13), 109 (14), 96 (12), 95 (100).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.96; H, 9.95.

(1α,3aβ,6aβ)-1-[2-(1,3-Dioxolan-2-yl)ethyl]hexahydro-3a,6a-dimethyl-2-oxopentalene-1-nitrile (36). A solution of 1.77 g (10 mmol) of α-cyano ketone **16** and 4.5 mL (29.5 mmol) of acrolein diethyl acetal in 35 mL of benzene was heated at reflux under nitrogen by using a Dean-Stark trap filled with molecular sieves to collect the condensate and return it to the flask.[45] The bath temperature was allowed to cycle between 104 and 115 °C. After 22 h the solution was cooled and concentrated. Purification of the residue was by chromatography on 120 g of silica gel and afforded 1.99 g (76%) of α-ethoxyallyl ketone **34** as a yellow oil: IR (film) ν_{max} 2990, 2250 (C≡N), 1755 (C=O), 1670 (sh), 1640 (C=C), 945 cm^{-1}; ^1H NMR (CCl_4) δ 1.13, 1.23 (2 s, 6 H, 2 CH_3), 1.26 (t, 3 H, J = 7 Hz, CH_3CH_2O), 1.5–2 (m, 6 H, $CH_2CH_2CH_2$), 2.32 (s, 2 H, CH_2CO), 2.33 (d, 2 H, J = 7 Hz, CH_2CH=CH), 3.7 (q, 2 H, J = 7 H, CH_3CH_2O), 4.6 (dt, J = 13, 7 Hz, CH_2CH=CH), 6.22 (d, 1 H, J = 13 Hz, CH=CHO).

A mixture of 1.86 g (7.1 mmol) of α-ethoxyallyl ketone **34**, 30 mL of ether, 30 mL of ethylene glycol, and 0.2 mL of concentrated hydrochloric acid was stirred vigorously at room temperature under nitrogen for 21 h. The reaction mixture was poured into 7% sodium bicarbonate and extracted with 1:1 ether–pentane. The combined organic extracts were washed with saturated sodium chloride, dried (Na_2SO_4), and evaporated. The yellow residue was filtered through 10 g of silica gel using 1:1 ether-pentane as eluant. Evaporation of the filtrate and cooling at −20 °C furnished 1.82 g (92%) of the keto acetal **36** as a white solid. Recrystallization from ether containing few drops of pentane gave the analytical sample: mp 79–80 °C; IR (CCl_4) ν_{max} 2230 (C≡N), 1740 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 1.21 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.5–2.2 (m, 10 H), 2.18 (AB, 2 H, J = 20 Hz, CH_2CO), 4.05 (m, 4H, OCH_2CH_2O), 5.03 (m, 1 H, OCHO).

Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.50;, H, 8.38; N, 4.97.

(3aα,6aα)-3-[2-(1,3-Dioxolan-2-yl)ethyl]-1,3a,4,5,6,6a-hexahydro-3a,6a-dimethyl-2-(trimethylsiloxy)pentalene (37). In a flame-dried, 250-mL, three-necked, round-bottomed flask equipped with a dry-ice condenser and a nitrogen inlet was placed 2.1 cm (13 mmol) of shiny lithium wire which had been previously washed with pentane. The flask was rapidly flushed with nitrogen and cooled to −78 °C. Ammonia (100 mL) was distilled from lithium into the flask, and the cooling bath was removed. To the resulting dark blue solution was added 1.53 g (5.5 mmol) of α-cyano ketone **36** in 24 mL of THF. After 20 min excess lithium was destroyed by dropwise addition of ca. 0.36 mL of 3-hexyne until the blue color was discharged. The ammonia was allowed to evaporate, and the last traces of solvent were removed at reduced pressure (0.3 mm). The remaining white solid was suspended in an additional 23 mL of fresh THF, and 3 mL of 1:1 chlorotrimethylsilane–triethylamine was added.[46] The mixture was stirred at room temperature for 2.5 h, poured into ice-cold 7% sodium bicarbonate, and extracted with two 5-mL portions of 1:1 ether–pentane. The combined organic extracts were washed with ice-cold saturated ammonia chloride and saturated sodium chloride before drying (Na_2SO_4). Distillation of the residual liquid in a Kugelrohr apparatus at 110–120 °C (0.3 mm) afforded 1.54 g (86%) of the enol silane (**37**): IR (film) ν_{max} 2950, 1690 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 0.17 (s, 9 H, $Si(CH_3)_3$), 1.0 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.2–2.1 (m, 10 H), 2.2 (br s, 2 H, CH_2C=C), 3.93 (m, 4 H, OCH_2CH_2O), 4.87 (t, 1 H, J = 4.5 Hz, $OCHOCH_2$).

Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94. Found: C, 66.51; H, 9.95.

(1α,3aβ,6aβ)-Octahydro-1,3a,6a-trimethyl-2-oxopentalene-1-propanoic Acid (38). A solution of 0.975 g (4.4 mmol) of keto aldehyde **6** in 15 mL of acetone was stirred at room temperature as 6 N chromic acid[42] was added dropwise at a rate such that each drop was consumed before the next drop was released. The reaction mixture remained pale orange after ca. 1 mL of chromic acid was added. After 10 min the orange color was destroyed by addition of ca. 0.2 mL of ethanol. The green reaction mixture was diluted with water and extracted with two 50-mL portions of ether. The combined ether layers were extracted twice with 7% sodium carbonate. The aqueous extracts were neutralized with concentrated hydrochloric acid and extracted twice with 1:1 ether–pentane. The combined organic extracts were washed with saturated sodium chloride, dried (Na_2SO_4), and evaporated. The liquid keto acid **38** (0.928 g, 92%) was used without further purification and had the following spectral properties: IR (film) ν_{max} 3100 (br, OH), 2950, 1740 (C=O), 1720 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 0.92, 0.99, 1.13 (3 s, 9 H, 3 CH_3), 1.3–1.9 (m, 8 H), 2.12 (ABd,2 H, CH_2CO), 2.0–2.85 (m, 2 H, CH_2CO_2H), 10.9 (br, 1 H, CO_2H).

(1α,3aβ,6aβ)-3,3a,4,5,6,6a-Hexahydro-2-hydroxy-1,3a,6a-trimethylpentalene-1-propanoic Acid Lactone (39). A solution of 0.928 g (3.9 mmol) of keto acid **38** in 15 mL of dichloromethane and 2 mL of (21 mmol) of acetic anhydride was stirred and cooled at 0 °C as 5 μL of perchloric acid was added.[27] The reaction mixture turned yellow-brown within 2 min. After 20 min ice and 6 mL of 7% sodium bicarbonate were added. When the evolution of carbon dioxide had ceased, the solution was diluted with 1:1 ether–pentane and added to ice-cold 7% sodium bicarbonate. The aqueous layer was extracted with ether–pentane. The combined organic layers were washed with saturated sodium chloride, dried (Na_2SO_4), and evaporated. Purification of the residue by preparative TLC with 20% ethyl acetate–pentane as developing solvent afforded 0.613 g (64%) of the enol lactone (**39**) as a colorless solid: mp 72.5–73 °C; IR (CCl_4) ν_{max} 2950, 1750 (C=O), 1715 (sh), 1660 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 1.0, 1.17, 1.22 (3 s, 9 H, 3 CH_3), 1.3–2.2 (m, 10 H), 4.94 (s, 1 H, CH=C).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.31; H, 9.15. Found: C, 76.32; H, 9.07.

(1aα,3aβ,6aβ)-Hexahydro-1,3a,6a-trimethyl-1-[3-oxo-4-(phenylthio)-butyl]-2(1*H*)-pentalenone (41). To an ice-cold solution of 0.118 mL (1 mmol) of thioanisole and 0.115 g (1 mmol) of diazabicyclooctane in 1.5 mL of THF was added 0.48 mL (1.10 mmol) of 2.3 M *n*-butyllithium in hexane.[47] The cooling bath was removed, and the solution was stirred for 1 h. A 0.5-mL (0.28-mmol) aliquot of the resulting solution of ((phenylthio)methyl)lithium was added to a solution of 41 mg (0.18 mmol) of diketone **29** in 0.5 mL of THF which was stirred and cooled at −78 °C. The reaction mixture was allowed to warm to −30 °C over 2 h, after which 0.5 mL of 7% sodium bicarbonate was added. The mixture was poured into 7% sodium bicarbonate and extracted with 1:1 ether–pentane. The combined extracts were washed with 1.2 N hydrochloric acid and saturated sodium chloride, dried (Na_2SO_4), and evaporated. Purification of the residue by preparative TLC using 30% ethyl acetate–hexane as developing solvent furnished 27 mg (55%) of α-phenylthio ketone **41** and 8 mg of recovered diketone **29**. The spectral properties of **41** are as follows: IR (film) ν_{max} 2980, 1745 (C=O), 1720 (sh), 1600 cm^{-1}; ^1H NMR (CCl_4) δ 0.96, 0.99, 1.20 (3 s, 9 H, 3 CH_3),

(45) The Dean-Stark trap and molecular sieves were used to remove water and/or ethanol formed in the reaction. However, only a small amount of water was collected, and satisfactory yields were obtained in later runs when the Dean-Stark trap was not employed.

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1.3–2.2 (m, 8 H), 2.22 (ABd, 2 H, ring CH_2CO), 2.3–3.2 (m, 2 H, chain CH_2CO), 3.70 (s, 2 H, CH_2S), 7.3–7.7 (m, 5 H, C_6H_5).

(3aα,4α,8α,8aα,9α)- and (3aα,4α,8α,8aα,9β)-Octahydro-9-hydroxy-3a,8,8a-trimethyl-4,8-methanoazulen-5(1*H*)-ones (42 and 43). This procedure was based in part on the method reported by Barton and co-workers.[34] A 1 M solution of lithium diisopropylamide was prepared by adding 10 mL (23 mmol) of 2.3 M *n*-butyllithium in hexane to a solution of 3.3 mL of diisopropylamine in 9.7 mL of THF at −78 °C. The solution was allowed to warm to room temperature and was stirred for 15 min. Aliquots of this solution were used as needed. If air and moisture are judiciously excluded, this solution can be kept in a refrigerator for as long as 1 month without appreciable decomposition. A suspension of 0.5 g (13.2 mmol) of lithium aluminum hydride in 5–6 mL of THF was stirred under nitrogen for 1 h and then allowed to settle for 4 h in a refrigerator. Aliquots of the supernatant solution were used as 5 N lithium aluminum hydride solution.

A degassed solution of 85 mg (0.39 mmol) of diketone **29** in 3 mL of THF was stirred and cooled at −78 °C as 0.39 mL (0.39 mmol) of 1 M lithium diisopropylamide in THF was added. After 15 min 0.4 mL (2.00 mequiv) of 5 N lithium aluminum hydride in THF was added. The mixture was stirred for 1.5 h at −78 °C at which time the dry-ice cooling bath was replaced by an ice bath. After 2.5 h at 0 °C, dry ammonia gas which had been distilled from sodium was bubbled into the reaction mixture to destroy the excess hydride. A 2-mL portion of 1.2 M hydrochloric acid was added, and the mixture was poured into 20 mL of 1:1 ether–pentane and 10 mL of 1.2 N hydrochloric acid. The aqueous layer was extracted with ether–pentane. The combined organic layers were washed with saturated sodium chloride, dried (Na_2SO_4), and evaporated. Purification of the residue by preparative TLC using 30% acetone–hexane as eluant provided 42.6 mg (50%) of a mixture of ketols **42** and **43**. The isomers were separated by a second preparative TLC purification using two developments with the same solvent. The yields and spectral properties were as follows: **42**, 21.6 mg (25%); IR (CCl_4) ν_{max} 3450 (OH), 2950, 1720 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 1.06, 1.12, 1.26 (3 s, 9 H, 3 CH_3), 1.3–1.9 (m, 8 H), 2.1–2.4 (m, 2 H, CH_2CO), 2.37 (s, 1 H, H at C-4), 3.89 (s, 1 H, C*H*OH); **43**, 13.6 mg (16%); IR (CCl_4) ν_{max} 3450 (OH), 2950, 1715 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 0.98 (s, 6 H, 2 CH_3), 1.08 (s, 3 H, CH_3), 1.1–2.2 (m, 10 H), 2.32 (d, ~1 H, J = 5 Hz, H at C-4), 4.11 (d, 1 H, J = 5.1 Hz, C*H*OH).

(3aα,4α,8α,8aα)-1,2,3,3a,4,5,8,8a-Octahydro-3a,4,7,8a-trimethyl-4,8-methanoazulen-9-one ((±)-Isogymnomitrone, 45) and (3aα,4α,8α,8aα)-Decahydro-3a,4,8a-trimethyl-7-methylene-4,8-methanoazulen-9-one ((±)-Gymnomitrone, 46). A solution of 30 mg (0.14 mmol) of diketone **29** in 2 mL of freshly distilled ether was stirred and cooled at −78 °C under nitrogen as 0.2 mL (0.14 mmol) of 0.7 M methyl lithium in ether was added. Stirring and cooling a −78 °C were continued for 4 h after which 0.5 mL of saturated ammonium chloride solution was added and the cooling bath was removed. When the ice had melted, the reaction mixture was added to a separatory funnel containing 30 mL of 1:1 ether–pentane and 15 mL of ice-cold saturated ammonium chloride solution. The aqueous layer was extracted with ether–pentane. The combined organic extracts were washed with saturated sodium chloride, dried (Na_2SO_4), and concentrated. The concentrated filtrate was passed over silica gel using additional ether as eluant to yield 24.4 mg (76%) of **(3aα,4α,5β,8α,8aα)-decahydro-7-hydroxy-3a,4,7,8a-tetramethyl-4,8-methanozulen-9-one (44)** as a white solid: IR (CCl_4) ν_{max} 3400 (OH), 2950, 1730 (C=O) cm^{-1}; ^1H NMR (220 MHz, CCl_4) δ 0.75, 0.82, 0.90, 1.18 (4 s, 12 H, 4 CH_3), 1.25–1.55 (m), 1.6–1.85 (m), 1.85 (s, 1 H, H at C-4), 1.9–2.4 (m, 2 H), 2.96 (td, J = 6, 12 Hz, endo H at C-3?); mass spectrum, m/e (relative intensity) 236 (M^+, 40), 221 (13), 194 (36), 165 (94), 137 (40), 124 (45), 109 (47), 95 (100); exact mass calcd for $C_{15}H_{24}O_2$ m/e 236.1770, found m/e 236.1778. When this procedure was carried out on larger scale with 92 mg (0.43 mmol) of diketone **29** and 0.6 mL (0.42 mmol) of ethereal methyllithium, a retroaldol ring opening occurred and 42 mg (44%) of diketone **33** was isolated after purification by preparative TLC.

A 0.2-mL (2.2-mmol) portion of phosphorous oxychloride was added to a solution of 24.4 mg (0.1 mmol) of ketol **44** in 2 mL of pyridine, and the resulting solution was heated at reflux under nitrogen for 2.5 h.[35] The reaction mixture was cooled, diluted with 1:1 ether–pentane, and poured into 1.2 N hydrochloric acid. The aqueous layer was extracted with ether–pentane, the combined organic extracts were washed with saturated sodium chloride and dried (Na_2SO_4), and the filtrate was evaporated. Purification of the residue by chromatography on 10 g of silica gel impregnated with 10% silver nitrate using 10% ethyl acetate–hexane as eluant gave 14.4 mg (64%) of a mixture of β,γ-enones **45** and **46**: ^1H NMR (CCl_4) δ 0.77, 0.79, 0.85, 0.87, 0.92, 0.92 (5 s, 9 H, 6 CH_3), 1.64 (d, ~1.5 H, J = 2 Hz, =CCH_3), 1.89 (s, ~0.5 H, H at C-4 in **45**), 2.49 (s, ~0.5 H, H at C-4 in **46**), 4.62 and 4.65 (2 s, ~1 H, =CH_2), 5.17 (br s, ~0.5 H, =CH). A GC analysis (column D, 140 °C) on the mixture showed two peaks in a ratio of 47:53 for **46** and **45**, respectively. The mixture of isomers was reduced without further purification.

(3aα,4α,8α,8aα,9α)-1,2,3,3a,4,5,8,8a-Octahydro-3a,4,7,8a-tetramethyl-4,8-methanoazulen-9-ol ((±)-Isogymnomitrol, 47) and (3aα,4α,8α,8aα,9α)-Decahydro-3a,4,8a-trimethyl-7-methylene-4,8-methanoazulen-9-ol ((±)-Gymnomitrol, (±)-1). To an ice-cold solution of 14.4 mg (0.065 mmol) of the mixture of β,γ-enones **45** and **46** in 2 mL of THF was added 8 mg (0.2 mmol) of lithium aluminum hydride under a nitrogen atmosphere. After 45 min at 0 °C excess hydride was destroyed by dropwise addition of 1 mL of 1.2 N hydrochloric acid. The reaction mixture was diluted with 1:1 ether–pentane and poured into ice-cold 1.2 N hydrochloric acid. The product was extracted with ether–pentane, the combined extracts were washed with saturated sodium chloride, and the solution was dried (Na_2SO_4) and evaporated. Purification of the residue by preparative TLC on a silica gel plate impregnated with 3% silver nitrate using 10% ether–pentane as developing solvent afforded 3.3 mg of (±)-isogymnomitrol (**47**), mp 60–64 °C, 2.5 mg of a 60:40 mixture of **47** and **1**, and 3.4 mg of (±)-gymnomitrol ((±)-**1**), mp 107–109 °C. The spectral properties of isomeric alcohols are as follows. **47**: IR (CCl_4) ν_{max} 3540 (OH), 2950, 1720 (C=C) cm^{-1}; ^1H NMR (220 MHz, CCl_4) δ 0.98, 1.04, 1.21 (3 s, 9 H, 3 CH_3), 1.66 (br s, ~3 H, C=CCH_3), 1.79 (s, 1 H, H at C-4), 2.26 and 1.93 (ABd, 2 H, J = 17.5 Hz, C=C-CH_2), 4.01 (s, 1 H, C*H*OH), 5.08 (br s, 1 H, C=CH); mass spectrum, m/e (relative intensity) 220 (M^+, 12), 205 (6), 124 (100), 123 (45), 109 (97), 107 (26), 95 (69), 81 (76); exact mass calcd for $C_{15}H_{24}O$ m/e 220.1821; found m/e 220.1824. (±)-**1**: IR (CCl_4) ν_{max} 3400 (OH), 2950, 1645 (C=C), 1060, 890 (C=CH_2) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) δ 0.96, 1.09, 1.24 (3 s, 9 H, 3 CH_3), 1.55 (s, 1 H, OH), 2.12 (2 d, 1 H, J = 7.17 Hz, allylic H), 2.33 (s, 1 H, H at C-4), 2.41 (m, 1 H, allylic H), 3.72 (s, 1 H, C*H*OH), 4.64 and 4.66 (2 s, 2 H, C=CH_2); mass spectrum: exact mass calcd for $C_{15}H_{24}O$ m/e 220.1821, found m/e 220.1821. The identity of the more polar component as (±)-gymnomitrol was established by peak-for-peak comparison of the IR (17 coincident peaks ±10 cm^{-1}) and NMR (all major peaks as well as fine structure) spectra with those of (+)-gymnomitrol.[22]

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Registry No. (±)-**1**, 71564-38-0; (±)-**5**, 80951-98-0; (±)-**6**, 72312-03-9; **7**, 32139-03-0; **8**, 21170-10-5; (±)-**9**, 80906-71-4; (±)-**10**, isomer 1, 80906-72-5; **10**, isomer 2, 80906-73-6; (±)-**11**, 80906-74-7; (±)-**12**, 72311-97-8; (±)-**13a**, 72317-88-5; (±)-(*E*)-**13b**, 80906-75-8; (±)-(*Z*)-**13b**, 80906-76-9; (±)-**14a**, 72311-98-9; (±)-**14a** alcohol, isomer 1, 80906-77-0; (±)-**14a** alcohol, isomer 2, 80906-78-1; (±)-**14b**, 80906-79-2; (±)-**14c**, 80906-80-5; (±)-**15a**, 80906-81-6; (±)-**15b**, 80906-82-7; (±)-**16**, isomer 1, 72319-88-1; (±)-**16**, isomer 2, 72311-99-0; (±)-**17**, 80906-83-8; (±)-**18**, 80906-84-9; (±)-**19**, 72312-19-7; (±)-**19** alcohol, isomer 1, 74629-83-7; (±)-**19** alcohol, isomer 2, 74629-84-8; (±)-**20**, isomer 1, 80906-85-0; (±)-**20**, isomer 2, 80906-86-1; (±)-**20** hydroxy ether, isomer 2, 80906-87-2; (±)-**20** hydroxy ether, isomer 2, 80906-88-3; (±)-**20** benzyloxy aldehyde, isomer 1, 80906-89-4; (±)-**20** benzyloxy aldehyde, isomer 2, 80906-90-7; (±)-**21**, isomer 1, 80906-91-8; (±)-**21**, isomer 2, 80906-92-9; (±)-**22**, 80906-93-0; **24**, 71519-52-3; (±)-**25**, 72346-50-0; (±)-**26**, 80906-94-1; (±)-**27**, 80906-95-2; (±)-**27** ketal alcohol, 80906-96-3; (±)-**28**, 72312-02-8; (±)-**29**, 72346-57-7; **30**, 80906-97-4; (±)-**31**, 80906-98-5; (±)-**32**, 80906-99-6; (±)-**33**, 71519-46-5; (±)-**34**, 72312-00-6; (±)-**36**, 72312-01-7; (±)-**37**, 80907-00-2; (±)-**38**, 72312-04-0; (±)-**39**, 72312-05-1; (±)-**41**, 80907-01-3; (±)-**42**, 80951-99-1; (±)-**43**, 72312-80-2; (±)-**44**, 80952-00-7; (±)-**45**, 72346-51-1; (±)-**46**, 71605-98-6; (±)-**47**, 71564-39-1; diethyl chlorophosphate, 814-49-3; butyl mercaptan, 109-79-5; thiophenol, 108-98-5; allyl bromide, 106-95-6; benzyl bromide, 100-39-0; acrolein, 107-02-8; methyl vinyl ketone, 78-94-4; methyl bromide, 74-83-9; acrolein diethyl acetal, 3054-95-3; [(phenylthio)methyl]lithium, 13307-75-0; tetramethyl octahydro-3a,6a-dimethyl-2,5-dioxo-1,3,4,6-pentalenetetracarboxylate, 21170-09-2.